Computational Anatomy

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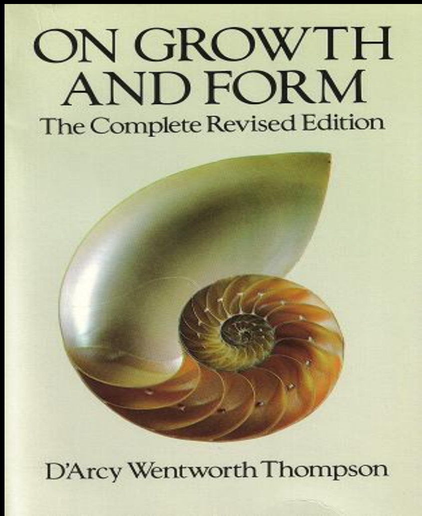
Computational Anatomy

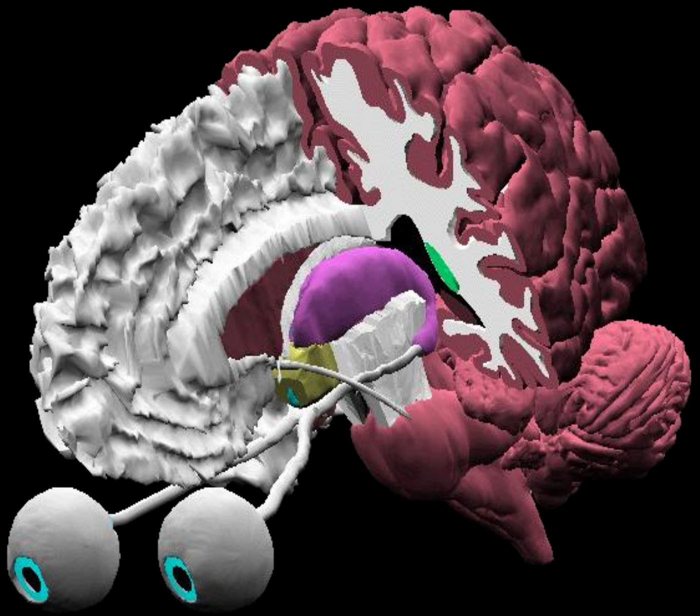
- origins found in D'Arcy Thompson's book *On Growth and Form*.
- focuses on the quantitative analysis of variability of biological shape
  - Analyze features derived from shape
    - e.g., lengths, angles, areas, volumes, etc

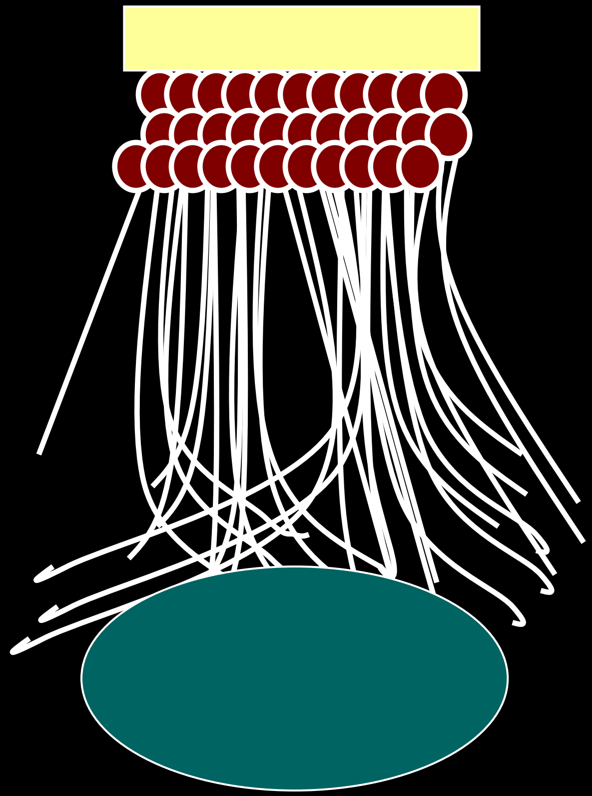


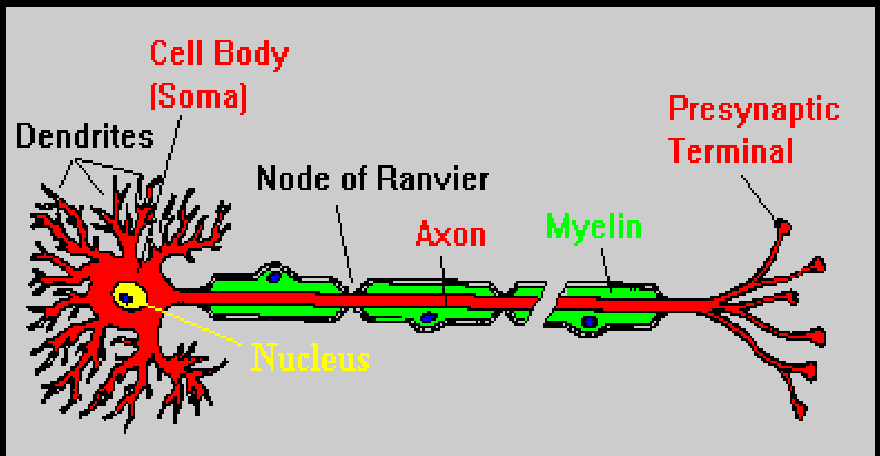
Challenge

- Clinical studies aim to describe effect of disease/treatment on brain
- Computational anatomy to quantify shape
  - Traditional volumetrics (regions of interest)
    - Tissue volumes
    - Manually delineated ROIs
    - Automated or semi-automated ROIs
  - Voxel based morphometry
  - Tensor and deformation morphometry
  - Surface morphometry (Duygu Tosun)

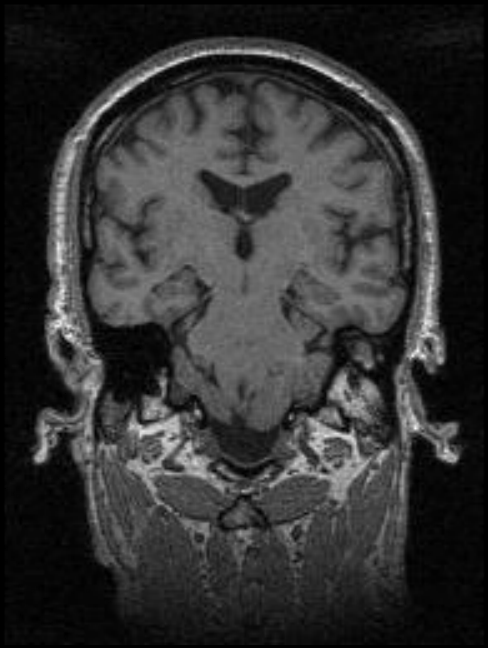
Neuron and Brain







Tissue Classification



T1-weighted MRI

Gray Matter

White Matter

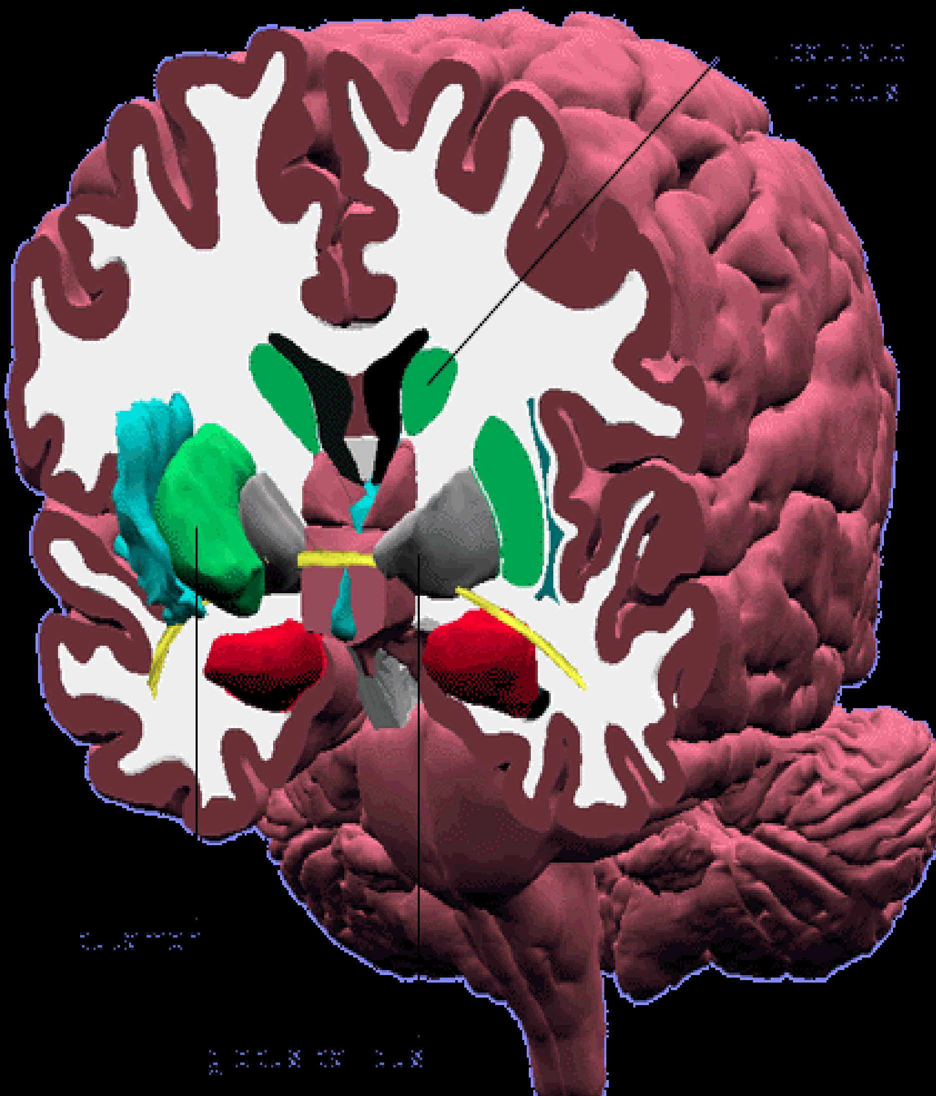
CSF

Lobar Regions of Interest (ROIs)

- Frontal Lobe
  - intelligence, behavior
  - motor control
- Parietal Lobe
  - sensory perception
  - language
- Occipital Lobe
  - vision
- Temporal Lobe
  - hearing, smell
  - language

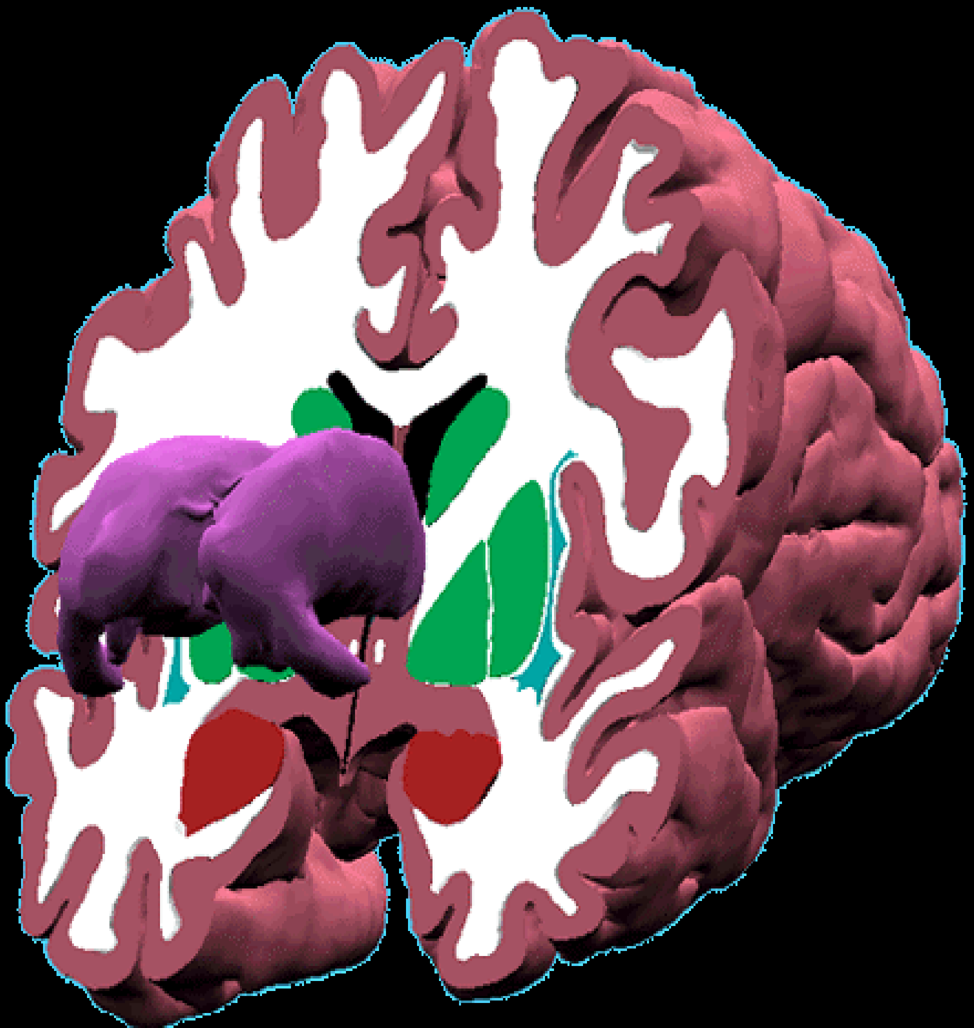
Basal ganglia

- Caudate
- putamen
- globus pallidus
- crude movement



Thalamus

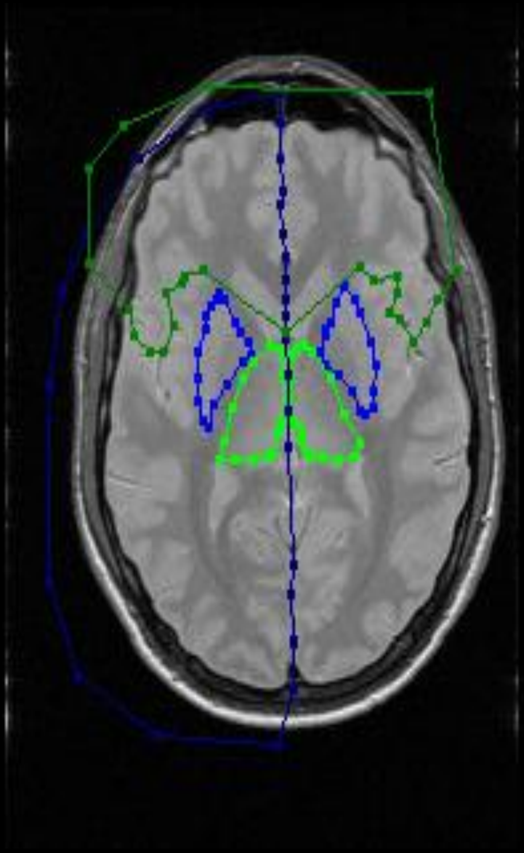
- Relay station
  - sensory
  - motor
- Connections to cortex



Hippocampus

- Learning
- Memory

Manual Subcortical Structure and Lobar Identification



Manual Hippocampal Identification

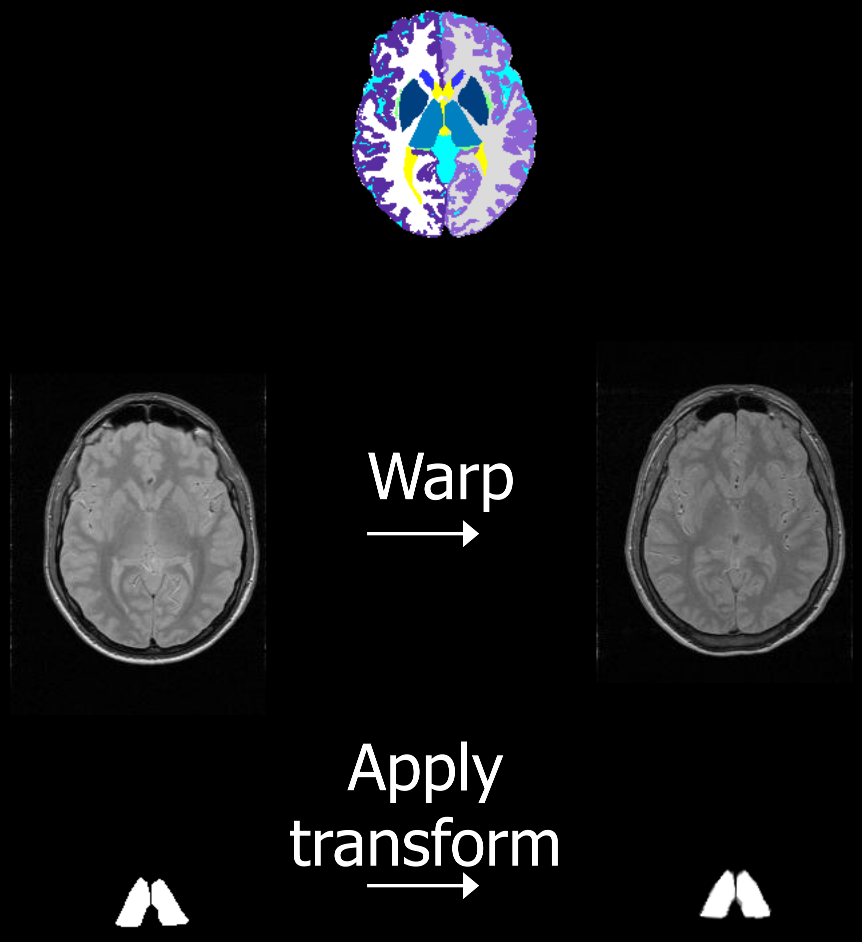
On each slice (approximately 29 to 32 slices for each side) a processor selects the hippocampus from head to tail

Problems

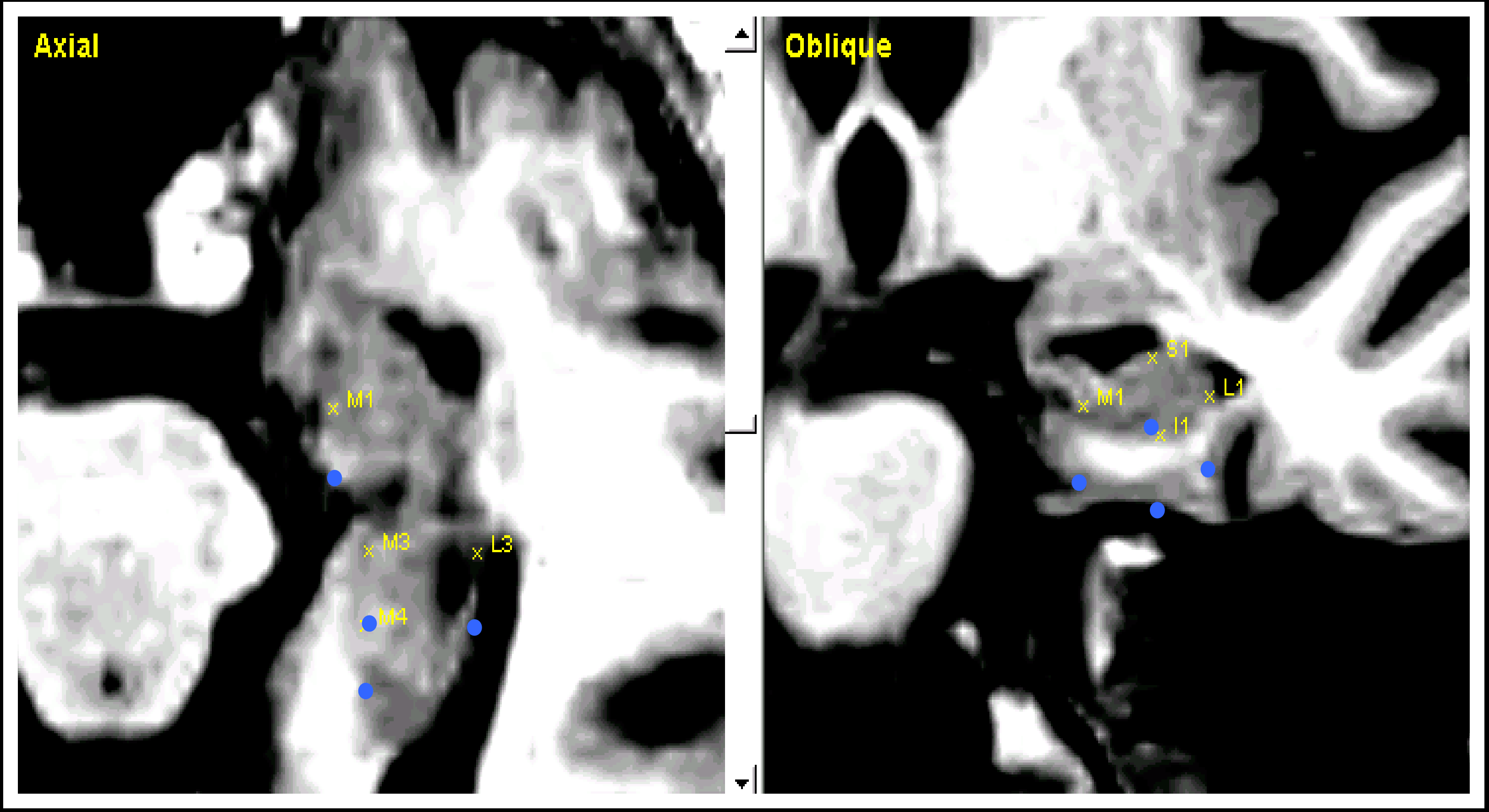
- Manual delineation
  - prone to error
  - High intra- and inter-rater reliability requires rigorous training
  - Enormous investment of time
- **Goal is to automate ROI identification**

Automatic ROIs

- Identify structures on template brain
- Warp template to new subject using gray scale images, sometimes landmark assisted
- Apply resultant transformation to template ROIs



Hippocampus: Landmarking

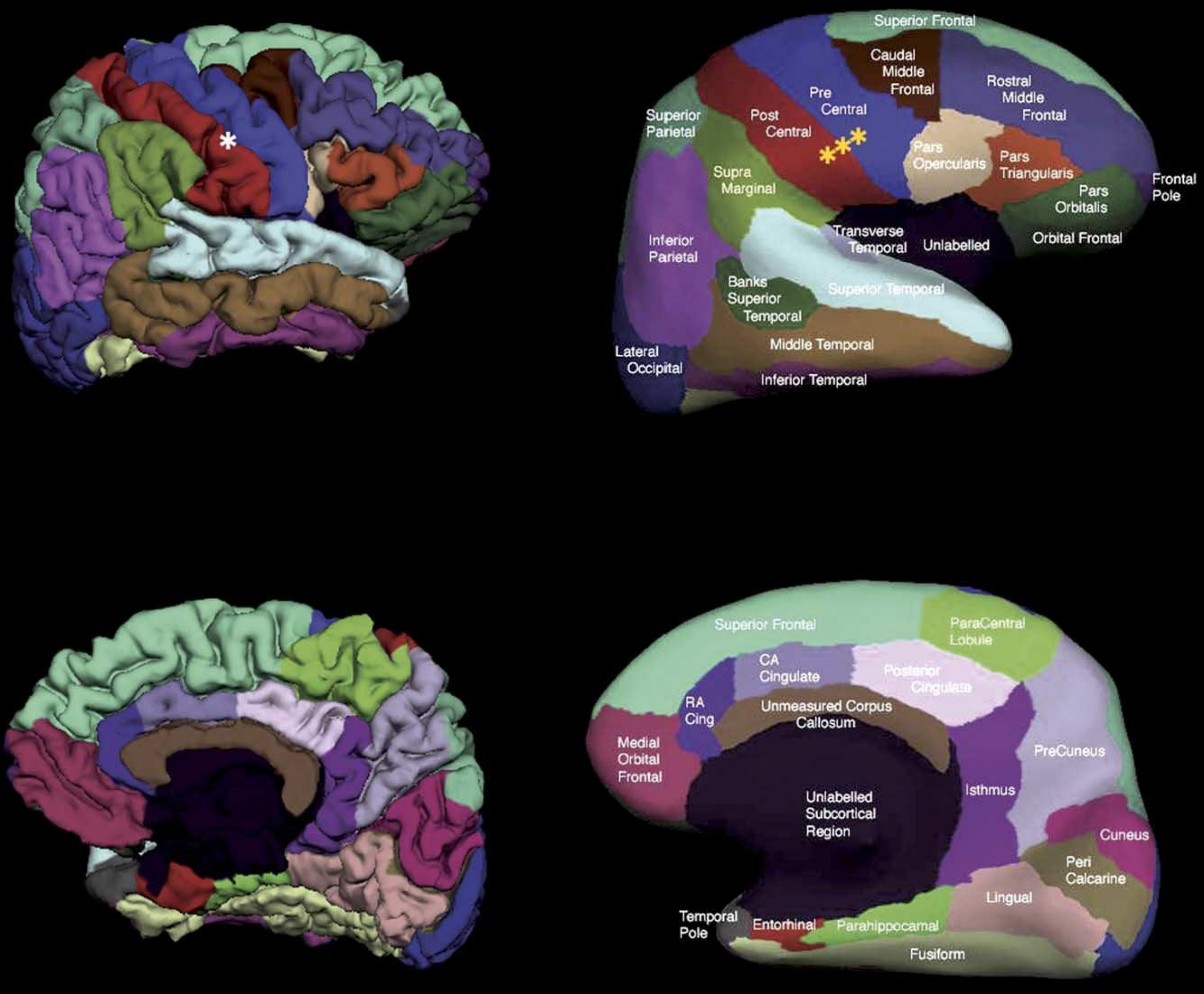


4 marks are placed on 5 slices along its length representing the width of the hippocampus (medial, inferior, lateral, superior)

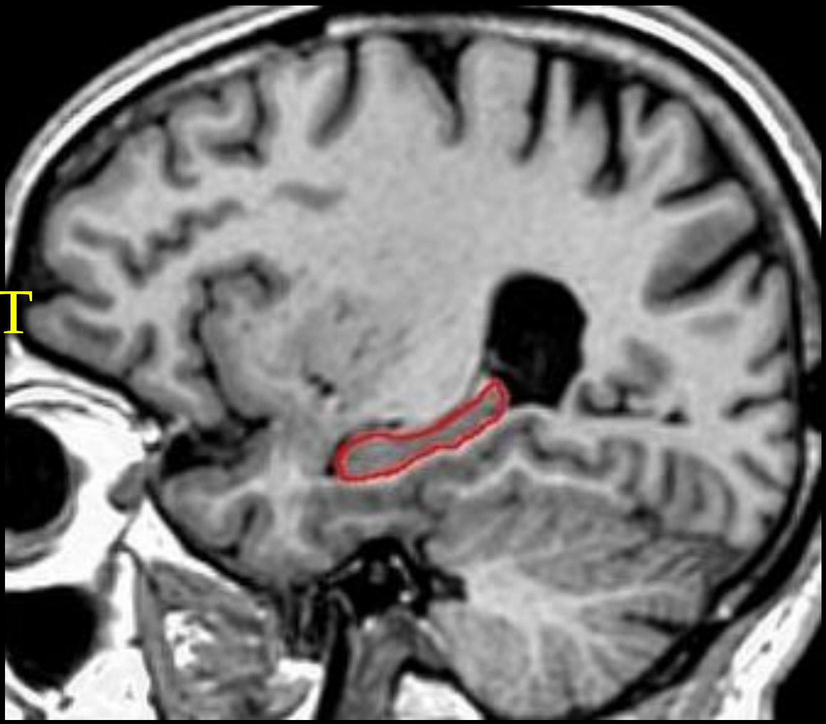
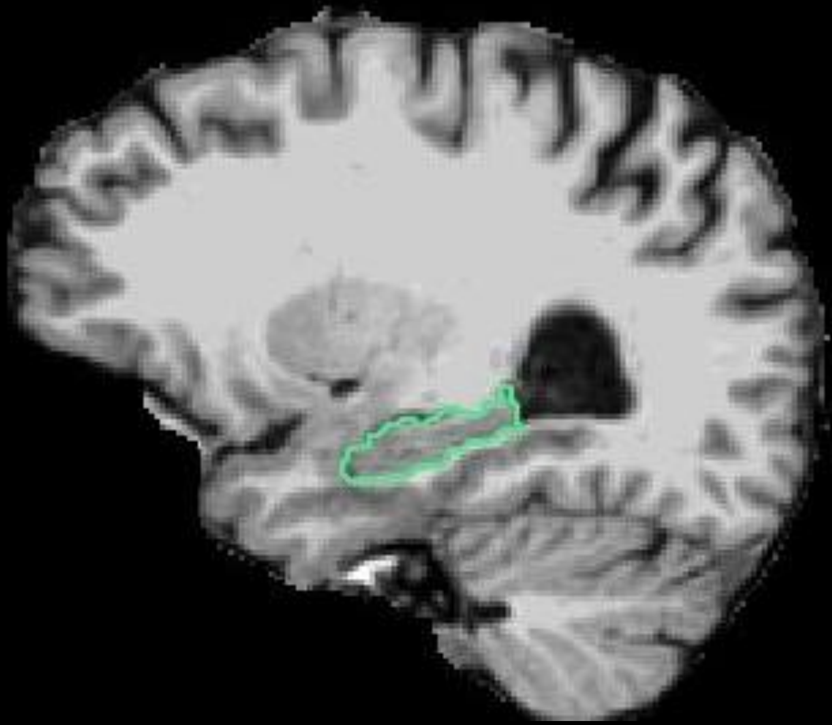
Automated Hippocampus Results

Result of landmarks and atlas being warped (represented here in coronal and axial views)

Freesurfer Cortical Parcellations



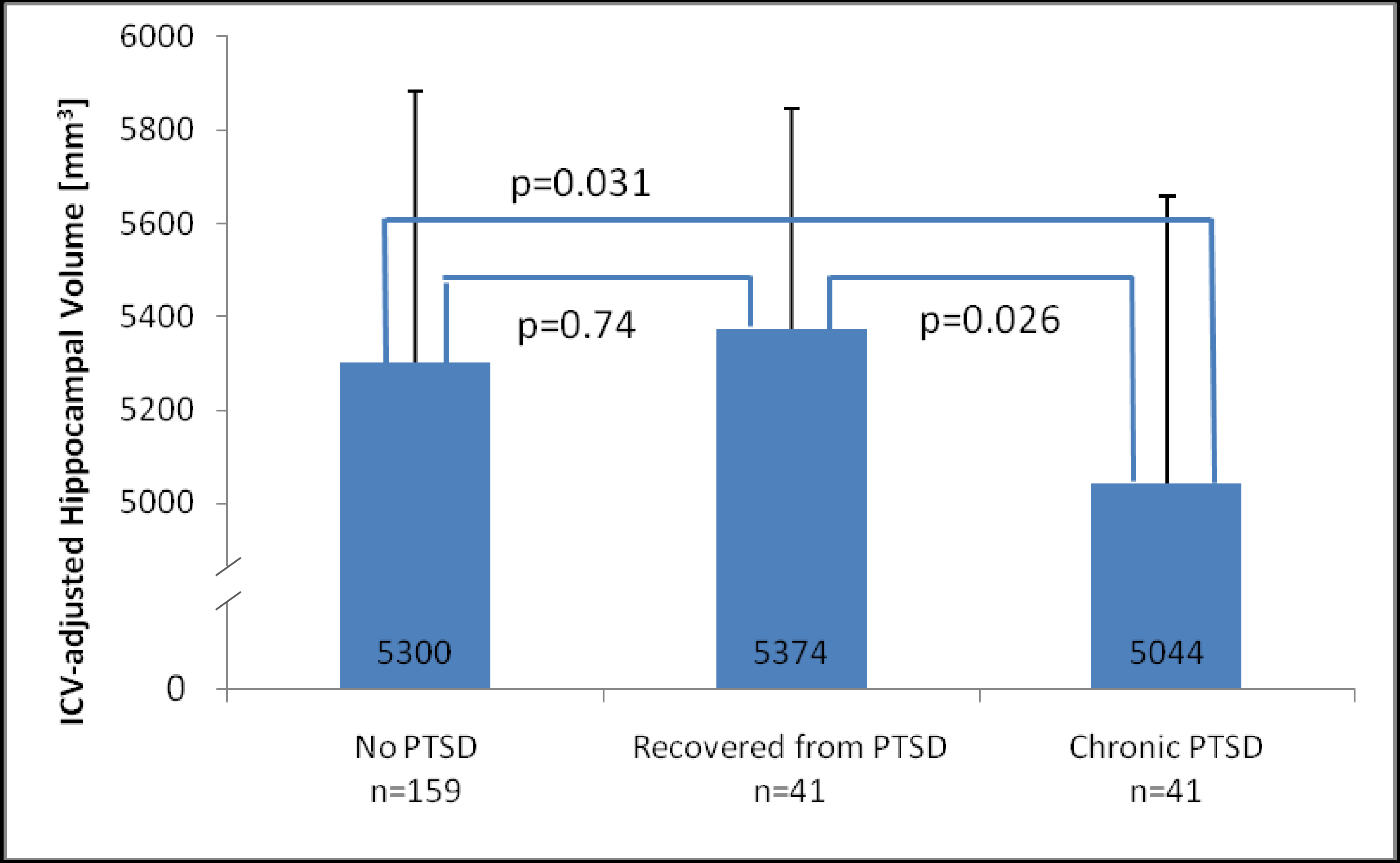
SNT vs Freesurfer Hippocampi

SNT   FS

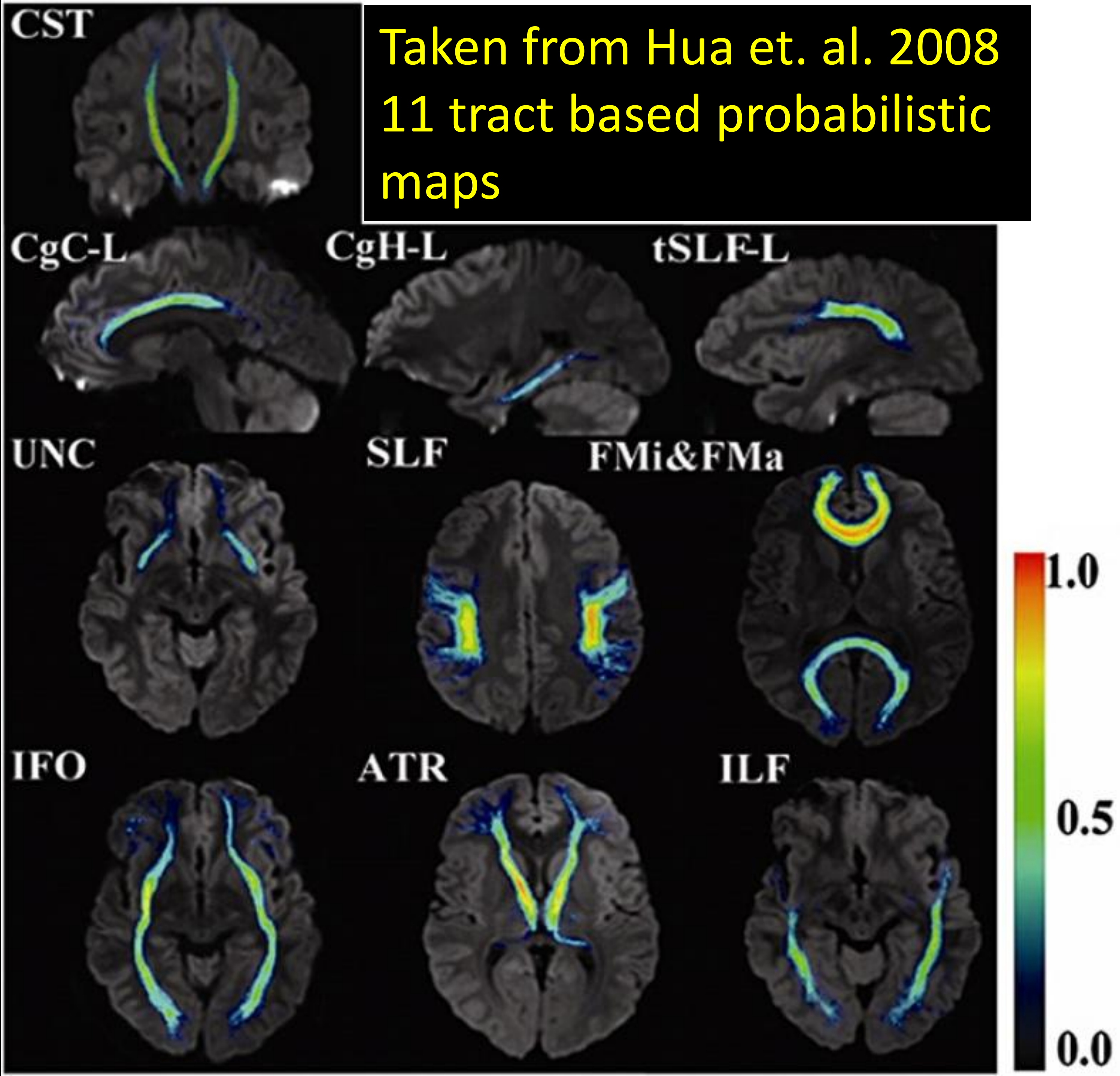
Method	Amygdala	Hippo GM	Fimbria / Alveus	Intralimbic Gyrus	Parahippo Gyrus
SNT	No	Yes	No	No	No
Freesurfer	Partial	Yes	Yes	Yes	Partial

Combining Tissue Classification and Automated ROIs (lobes, hippocampus)

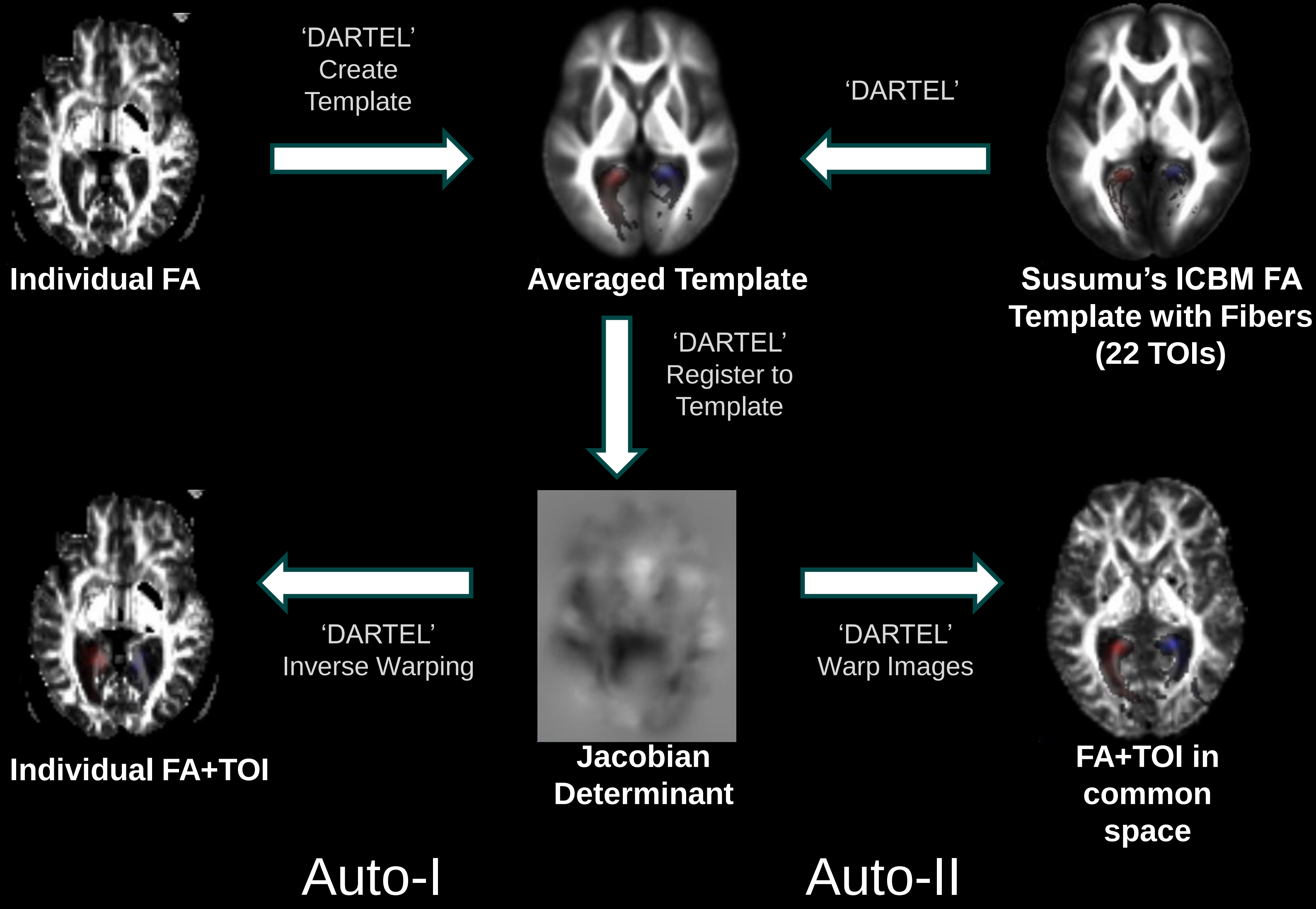
Comparison of hippocampal volume

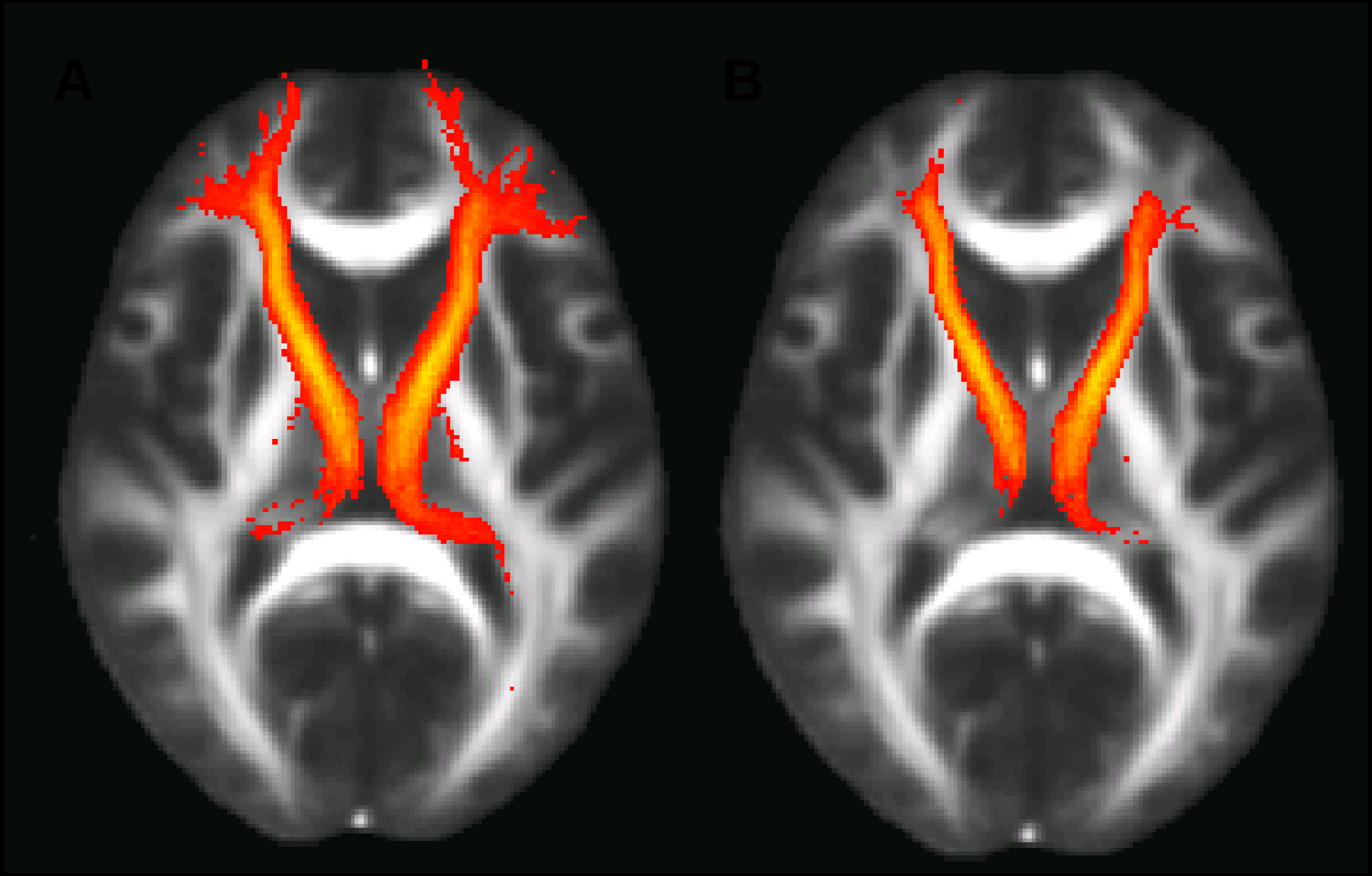


Taken from Hua et. al. 2008
11 tract based probabilistic maps



Auto Tract-of-Interest Measurement





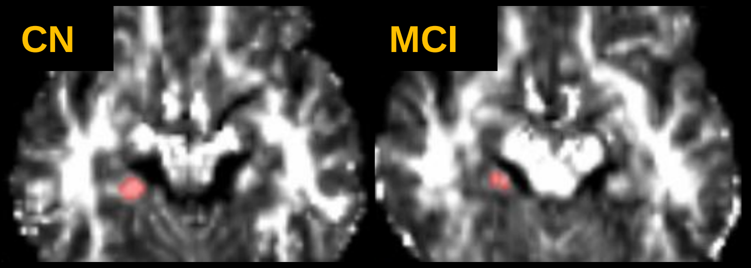
FA template image in MNI space with probabilistic tract-based ROIs of the anterior thalamic radiation (ATR) overlaid and thresholded at A) 5% and B) 20%

Auto-I findings in a large sample

92 subjects (32 CN / 30 AD / 30 MCI)

	CN (n=32)	**MCI** (n=30)	**aMCI** (n=15)	**AD** (n=30)	**MCI<CN** *p*	**aMCI<CN** *p*	**AD<CN** *p*
L. t.CG FA	0.36 (0.02)	0.36 (0.02)	0.35 (0.02)	0.33 (0.03)	n.s.	n.s.	<0.001
R. t.CG FA	0.37 (0.03)	0.37 (0.02)	0.37 (0.02)	0.34 (0.03)	n.s.	n.s.	<0.001
L. t.CG Vol [‰]	0.98 (0.15)	0.91 (0.13)	0.88 (0.12)	0.77 (0.15)	0.04	0.03	<0.001
R. t.CG Vol [‰]	1.10 (0.21)	1.04 (0.14)	1.02 (0.12)	0.84 (0.17)	n.s.	n.s.	<0.001

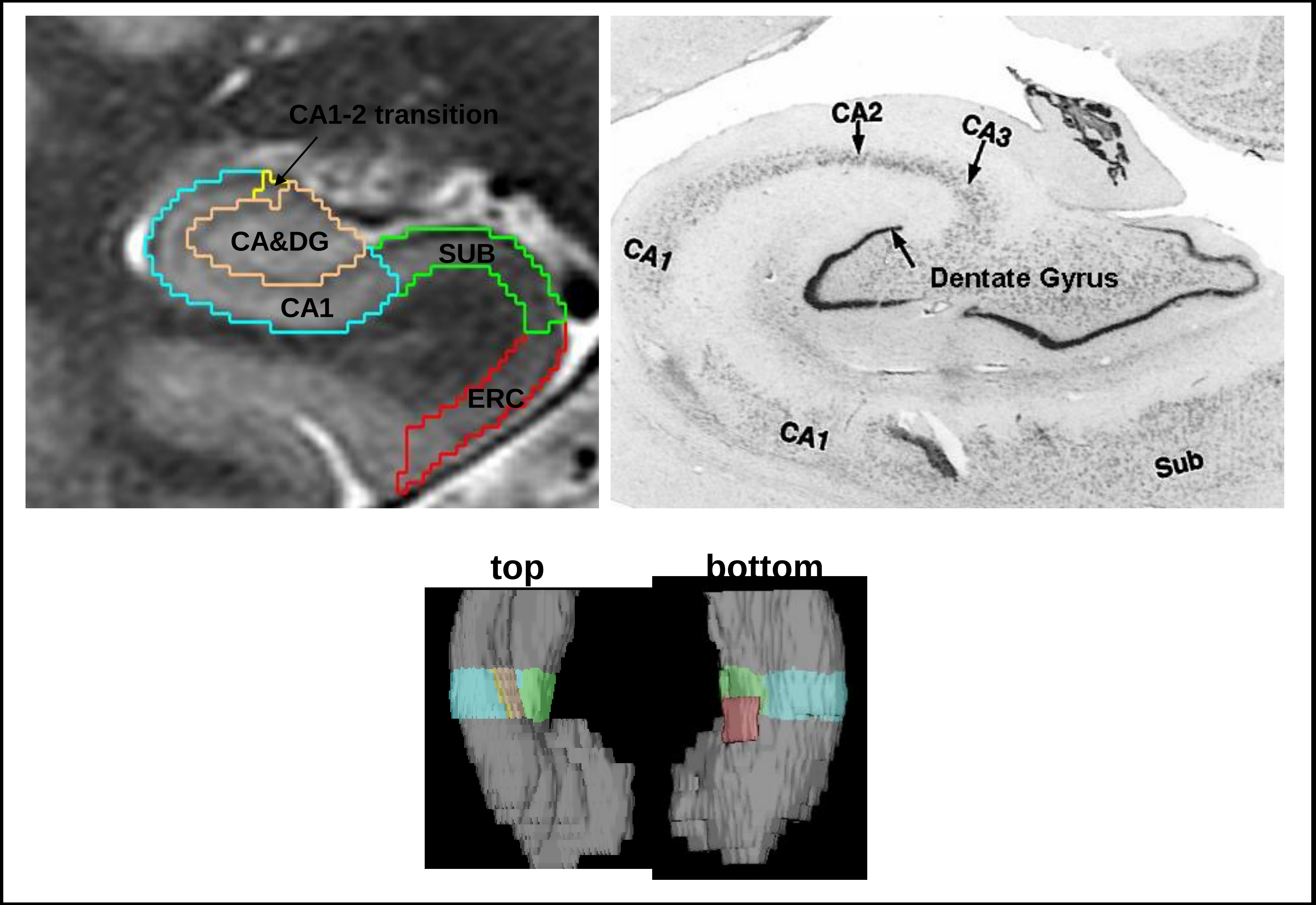
— Mean FA and fiber volume of the bilateral t.CG were significant reduced in AD vs. CN
— In MCI vs. CN: No difference of mean FA was seen; but left t.CG were significantly atrophied



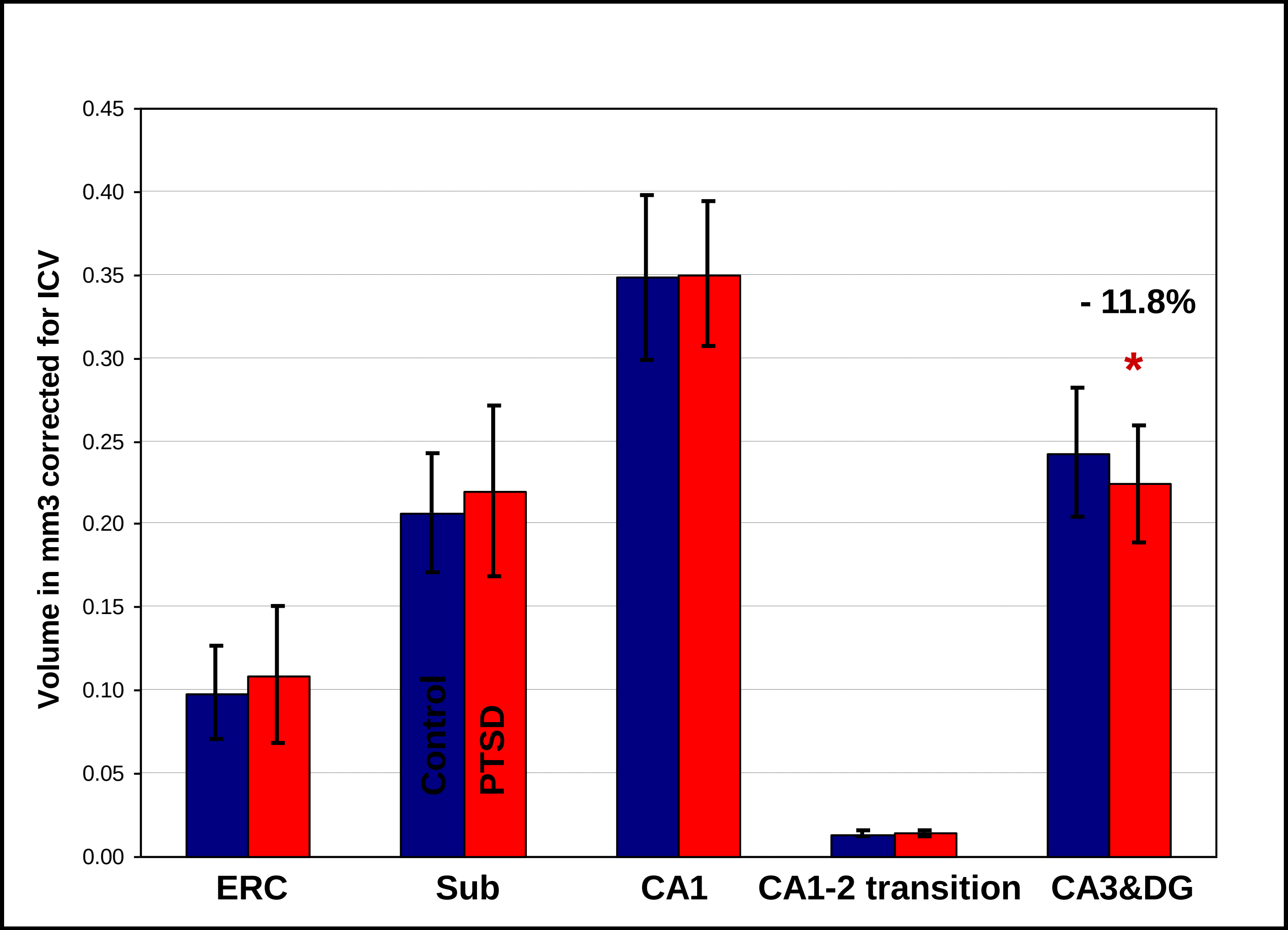
Limitations of Traditional Volumetrics

- User must choose ROIs *a priori*
- Disease or other clinical variable may affect a region of the brain not measured
- Common ROIs are affected by variety of diseases (low specificity)
- Effect may be localized; obscured in ROI
- Solutions:
  - Look at smaller ROIs (limit is voxel)
  - Identify *spatial pattern* of effects

Methods II: Manual Subfield Marking



Results I: PTSD Effect on Hippocampus



Wang et al. Arch Gen Psychiatry 2010, 67: 296 - 303

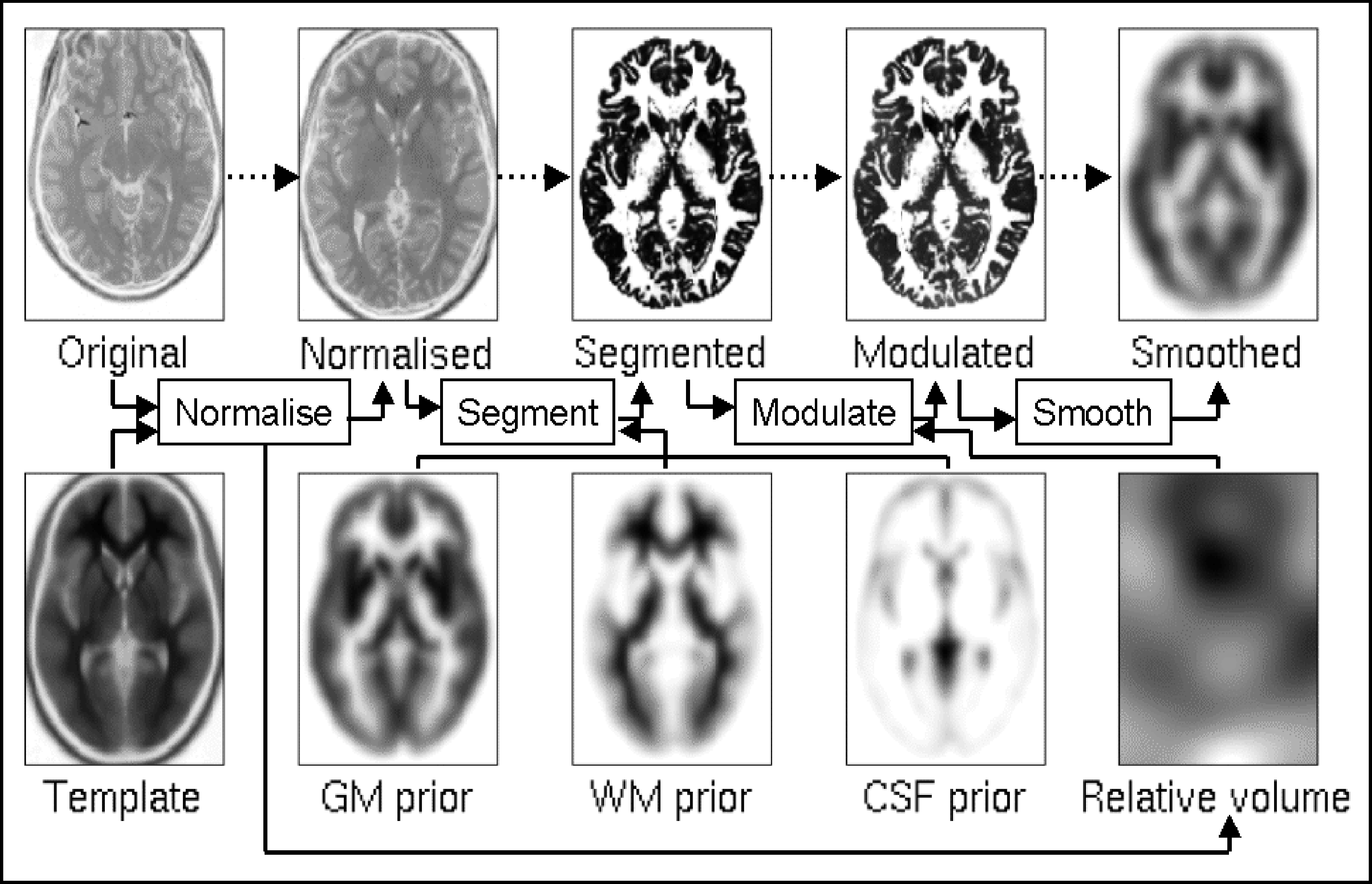
Voxel-Based/Deformation Morphometry

- Automated
- Suited for discerning patterns of structural change
- Explore location and extent of variation
- Use nonlinear registration or “warping” of images
  - Within: capture changes in brain over time
  - Between: measure deviation from atlas brain
  - relate anatomy to clinical/functional variables
- Statistics are computed on each voxel
- Low power

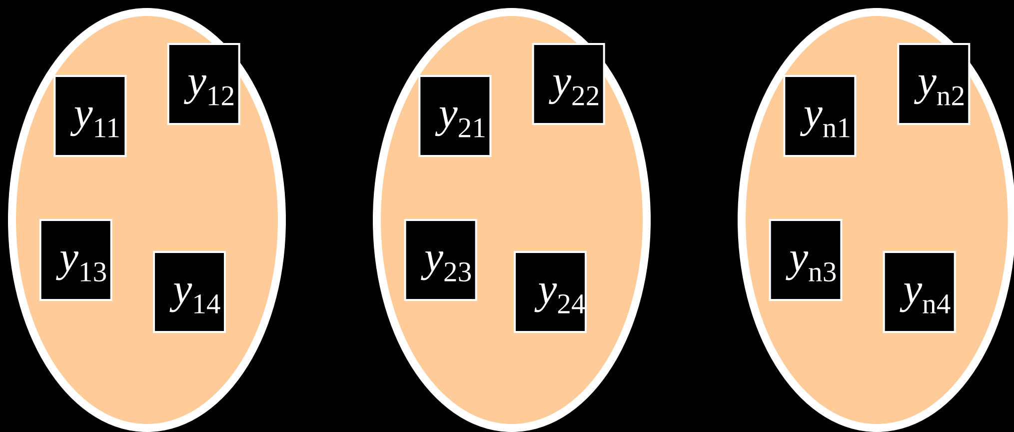
Voxel-wise Morphometry

- Produce a map of statistically significant differences among populations of subjects.
  - e.g. compare a patient group with a control group.
  - or identify correlations with age, test-score etc.
- Images are pre-processed so that corresponding regions of the brain are in spatial alignment

Pre-processing for Voxel-Based Morphometry (VBM)



Voxel-wise Statistics



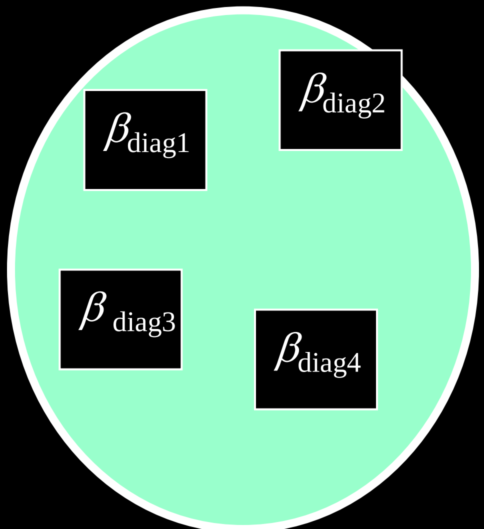
Map 1;
diagnosis 0
age 65
score 16

Map 2;
diagnosis 1
age 68
score 8

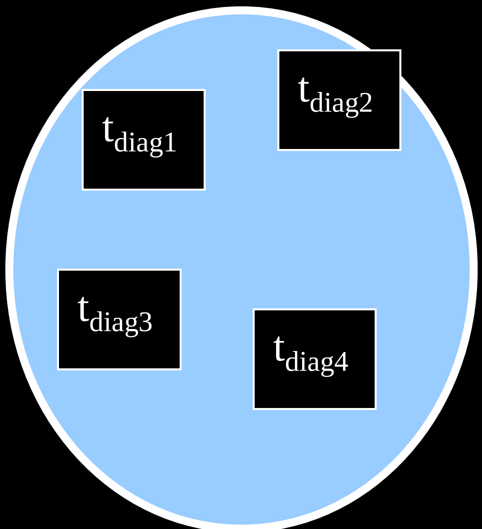
Map n;
diagnosis 1
age 73
score 4

$$\begin{bmatrix} y_{11} \\ y_{21} \\ \vdots \\ y_{n1} \end{bmatrix} = \begin{bmatrix} 0 & 65 & 16 & 1 \\ 1 & 68 & 8 & 1 \\ & & \ddots & \\ 1 & 73 & 4 & 1 \end{bmatrix} \begin{bmatrix} \beta_{diag1} \\ \beta_{age1} \\ \beta_{score1} \\ \beta_{\mathrm{int}1} \end{bmatrix}$$

$$\begin{bmatrix} y_{12} \\ y_{22} \\ \vdots \\ y_{n2} \end{bmatrix} = \begin{bmatrix} 0 & 65 & 16 & 1 \\ 1 & 68 & 8 & 1 \\ & & \ddots & \\ 1 & 73 & 4 & 1 \end{bmatrix} \begin{bmatrix} \beta_{diag2} \\ \beta_{age2} \\ \beta_{score2} \\ \beta_{\mathrm{int}2} \end{bmatrix}$$

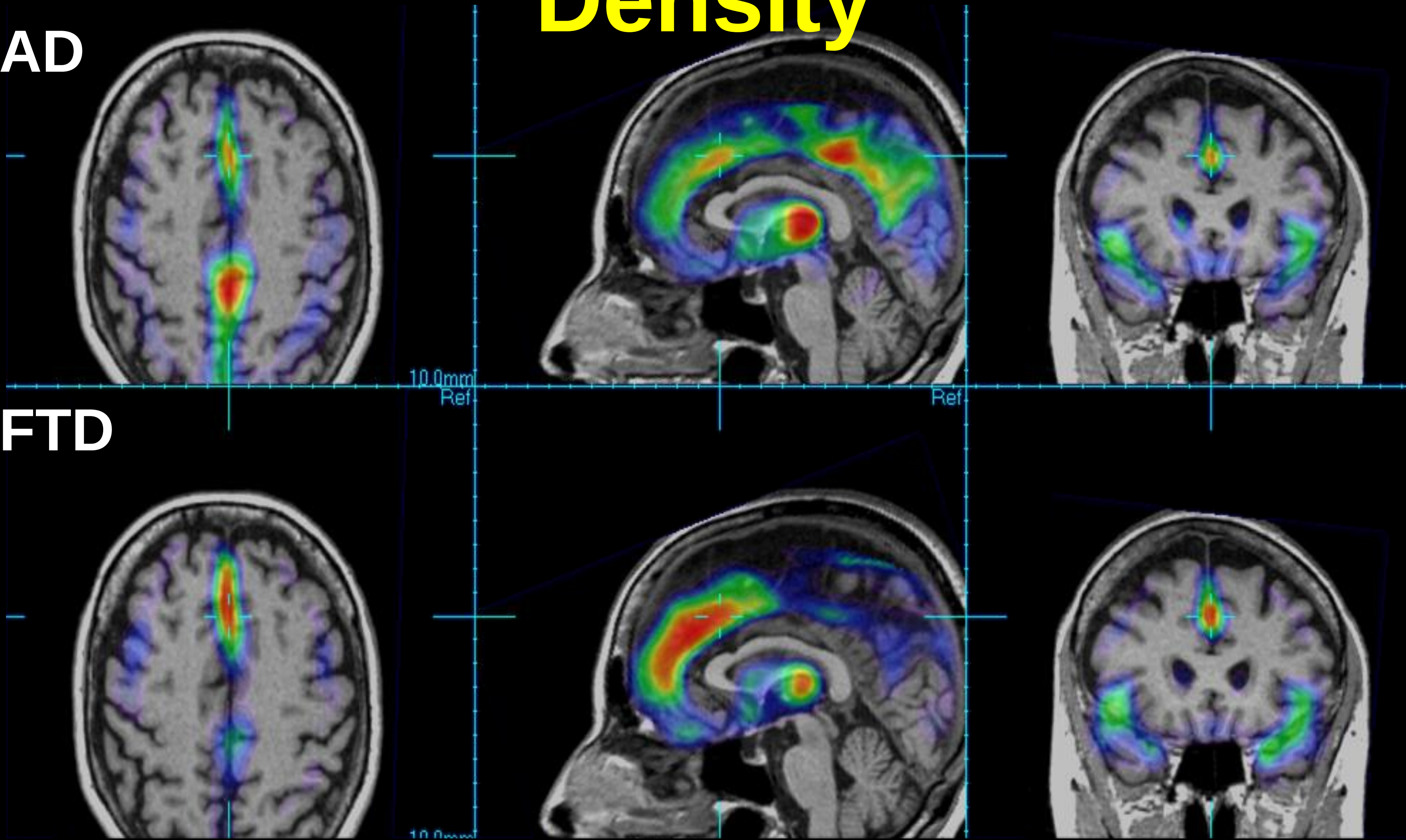


coefficient maps for each variable



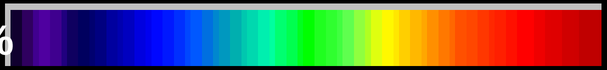
statistic maps for each variable

AD and FTD Gray Matter Density



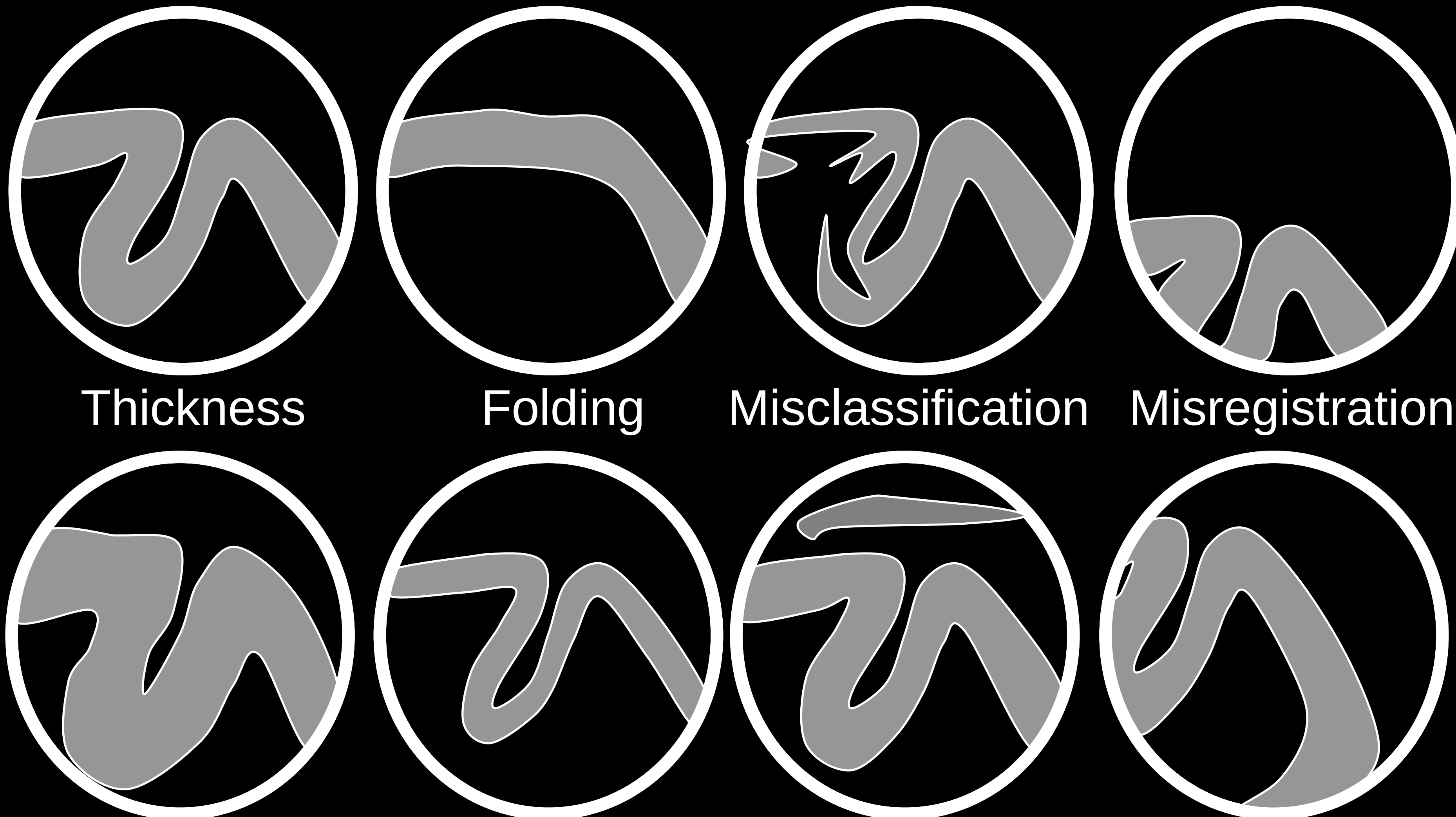
Reduction in Mean Local Gray Matter Density

12mm Gaussian Density Filter

5%  20%

20mm B-Spline Warp

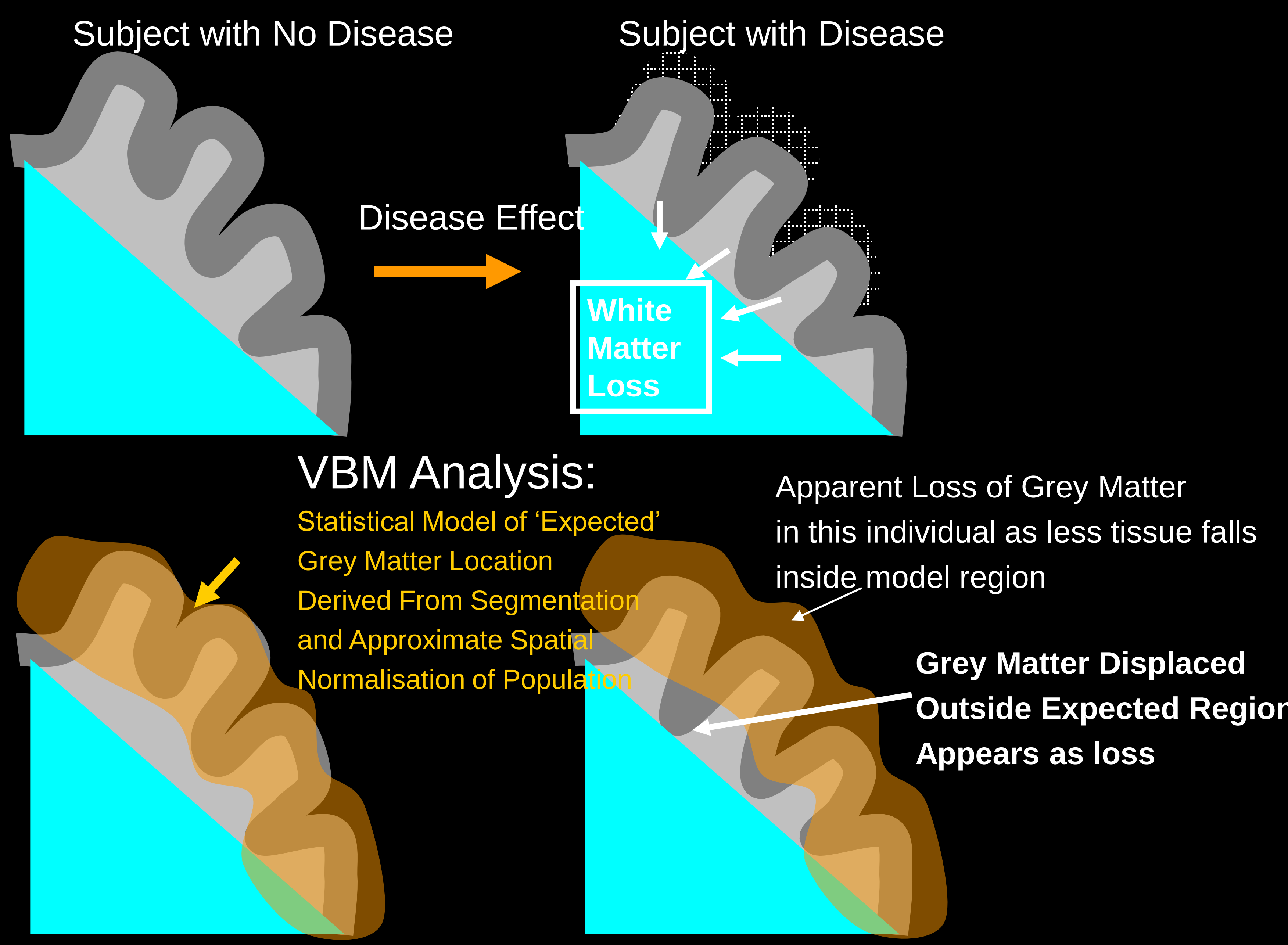
Some Explanations of the Differences



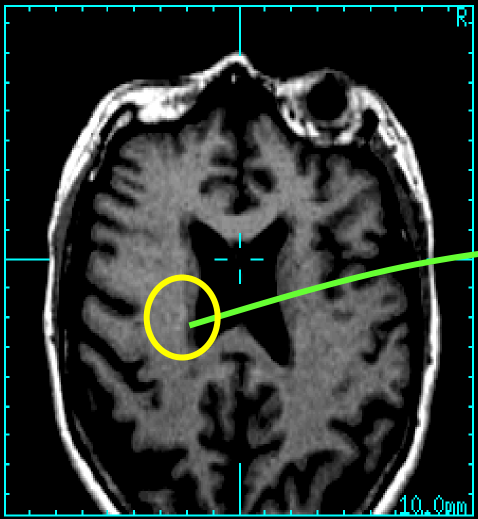
Limitations of VBM

- Voxel based morphometry (VBM)
  - confuses tissue volume loss and displacement
  - relies on the automated segmentation of images
  - regions of abnormal WM may be incorrectly classified as GM
  - segmentation of subcortical structures can be problematic due to mixing of GM and WM
- VBM is a flawed method for investigating white matter (WM) loss or subcortical involvement.

Ambiguities in Interpreting VBM results

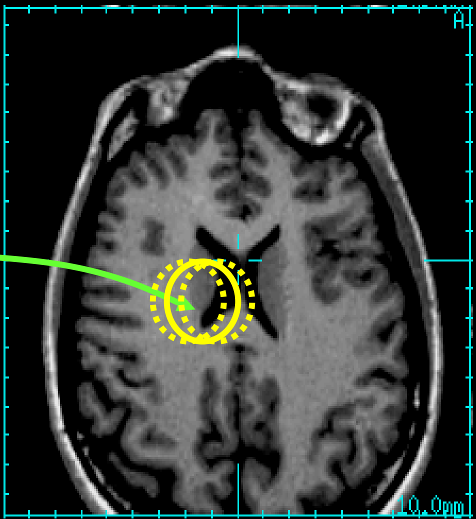


Comparing VBM to Deformation Morphometry

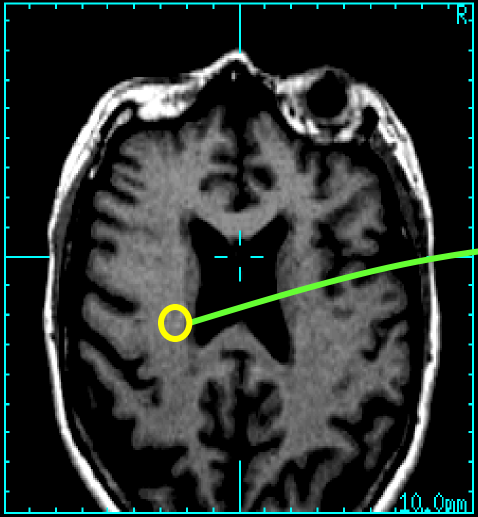


Coarse Non-Rigid Transformation

Compare Regional Stats: e.g. Gray Matter Density

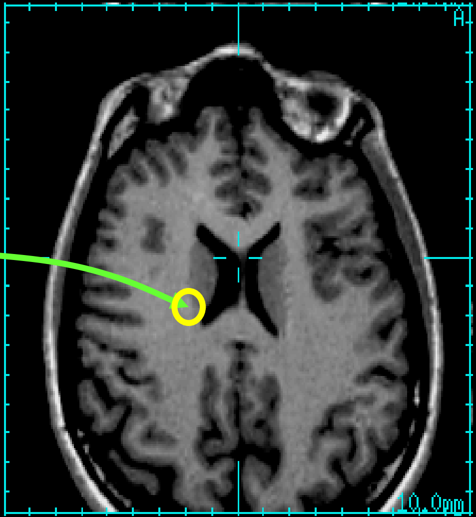


Voxel Morphometry



Fine+Accurate Nonlinear Transformation

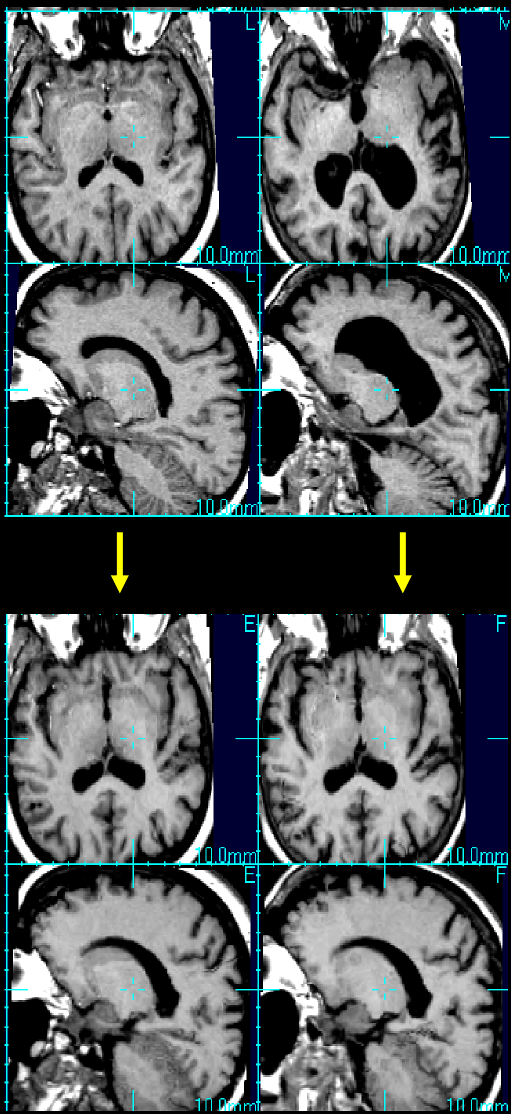
Transformation Describes All Differences



Deformation or Tensor Morphometry

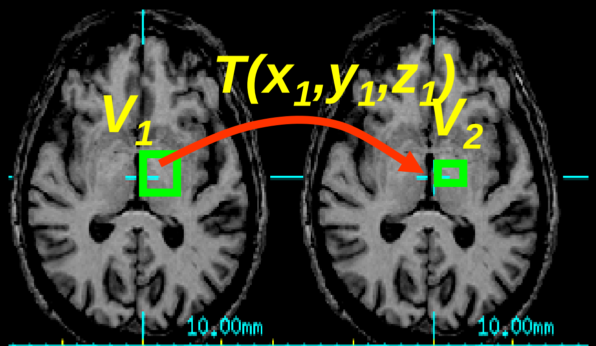
Creating Deformation Maps

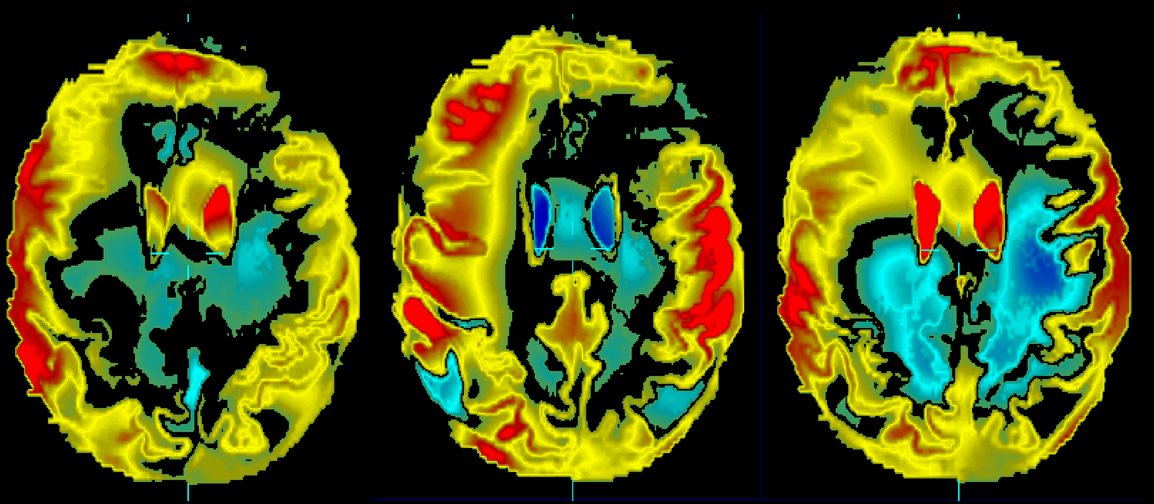
Step 1: Nonlinear Registration



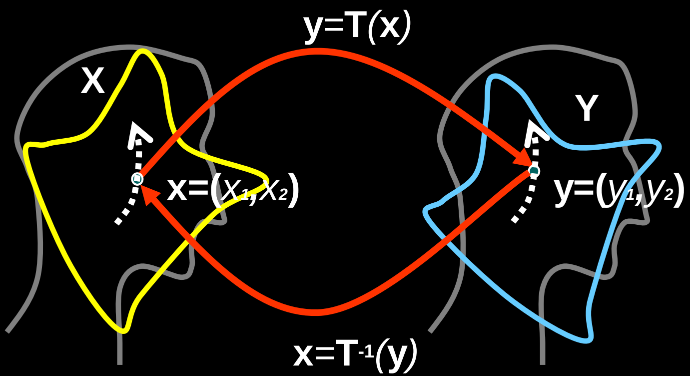
Step 2: Determinant of Jacobian Matrix at each voxel, giving the pointwise volume change at each point

$$\left|J(x_1,y_1,z_1)\right| = \begin{vmatrix} \dfrac{dx_1}{dx_2} & \dfrac{dx_1}{dy_2} & \dfrac{dx_1}{dz_2} \\ \dfrac{dy_1}{dx_2} & \dfrac{dy_1}{dy_2} & \dfrac{dy_1}{dz_2} \\ \dfrac{dz_1}{dx_2} & \dfrac{dz_1}{dy_2} & \dfrac{dz_1}{dz_2} \end{vmatrix} = \frac{V_1}{V_2}$$





More about the Jacobian

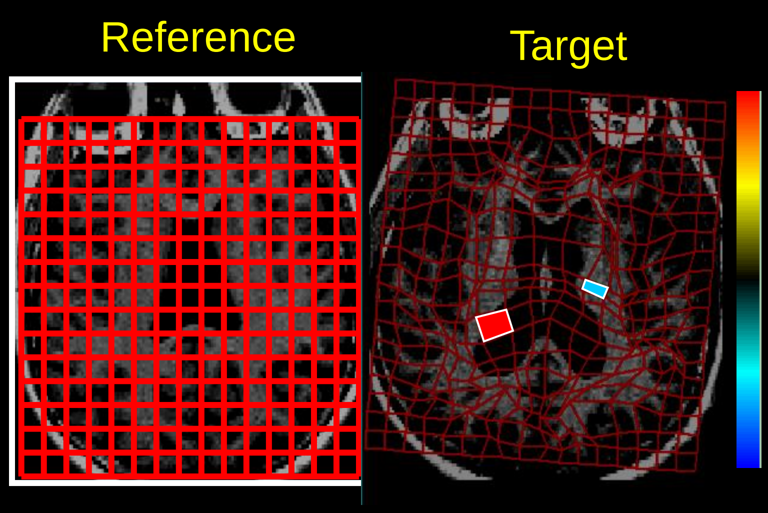


When moving in a path across one anatomy, how quickly are we moving in each axis in the other anatomy?

Summarized by the Jacobian Matrix of partial derivatives

$$\left|J(x_1, y_1, z_1)\right| = \frac{V_2}{V_1} > 1, \text{ voxel expansion}$$

$$\left|J(x_1, y_1, z_1)\right| = \frac{V_2}{V_1} < 1, \text{ voxel shrinkage}$$

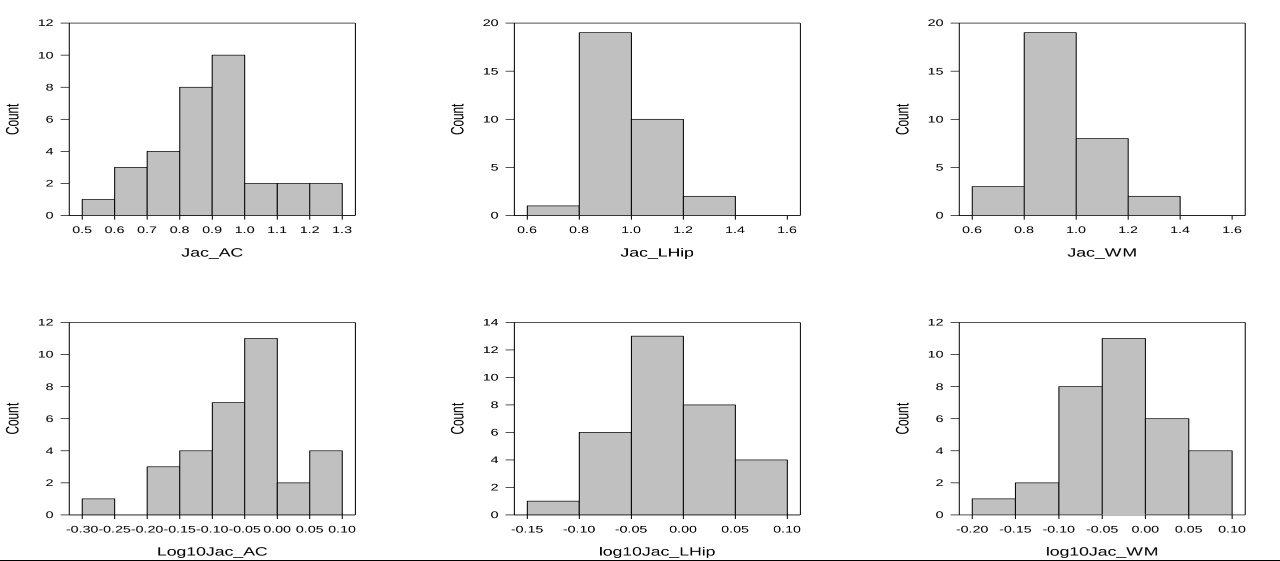


Jacobian or log Jacobian?

- $0 \leq |J| < \infty$; log transform normalizes distribution

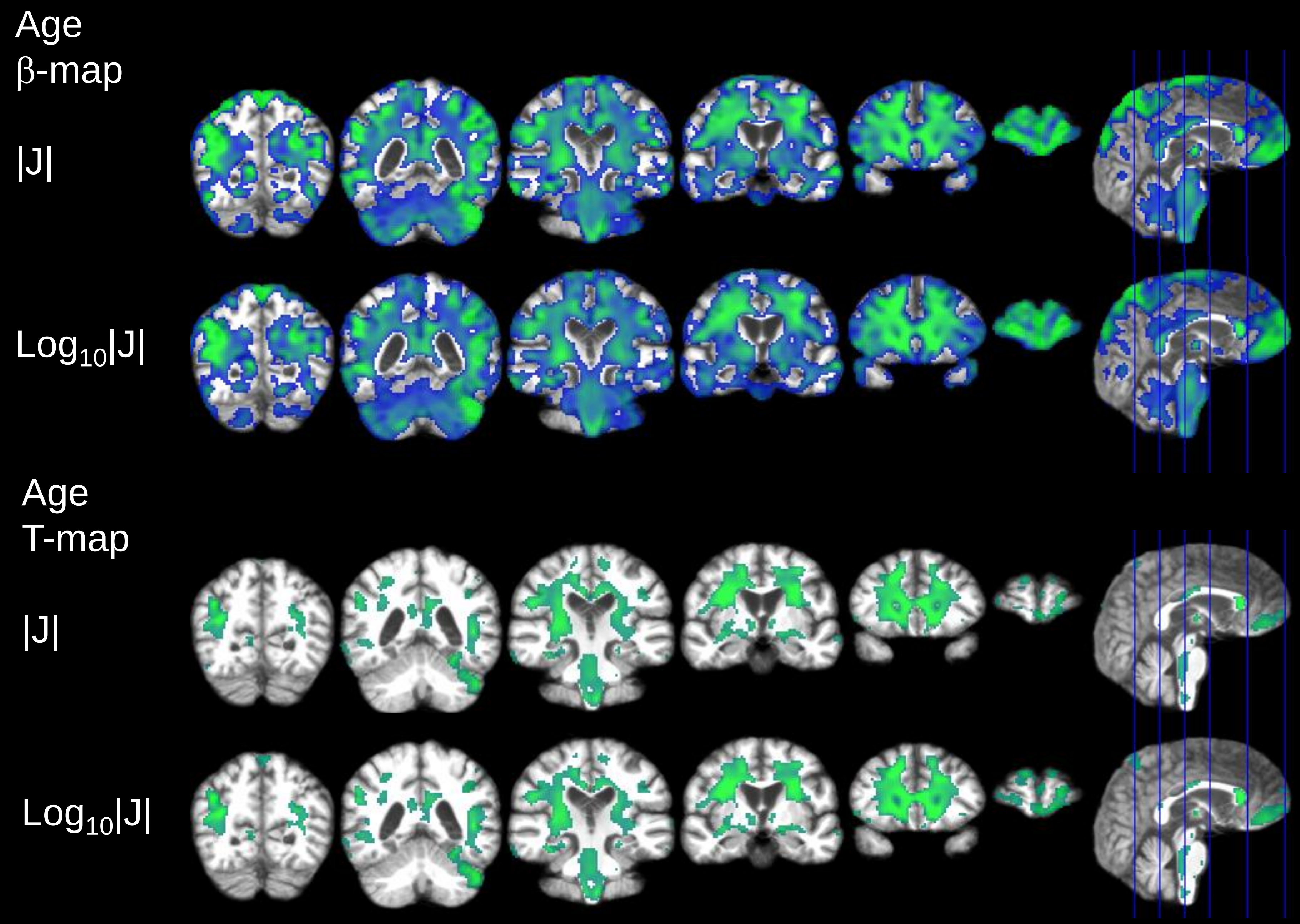
$|J|$

$\log_{10}|J|$



32 controls; all distributions pass tests for normality

- Equal probabilities to expansions and shrinkages that are reciprocals, i.e.
  - $|J|=0.5$, $\log_{10}|J|=-0.3$
  - $|J|=2.0$, $\log_{10}|J|= 0.3$



If your data are normal, choice of |J| or $\log_{10}$|J| matter of preference.

Group Comparisons of Between Subject Differences using Deformation Morphometry

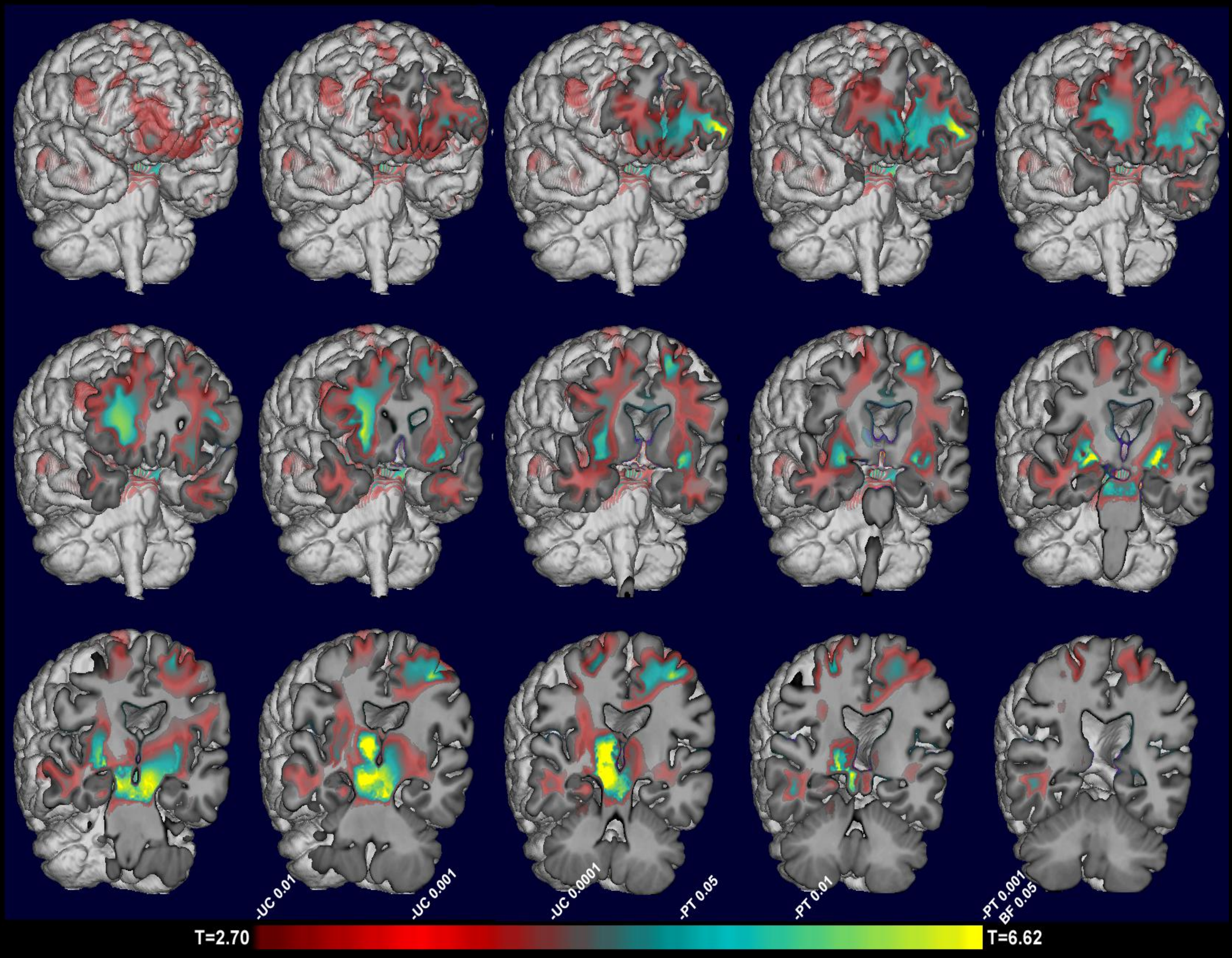
FTD

- Clinical subtype of frontotemporal lobar degeneration
- Impairment of personal conduct and social behavior
- Sometimes presents with ALS
- Postmortem studies show that atrophy:
  – begins in frontal lobe,
  – extends into the anterior temporal lobes and basal ganglia,
  – eventually involves subcortical structures,
  – white matter is prominently affected.

Methods

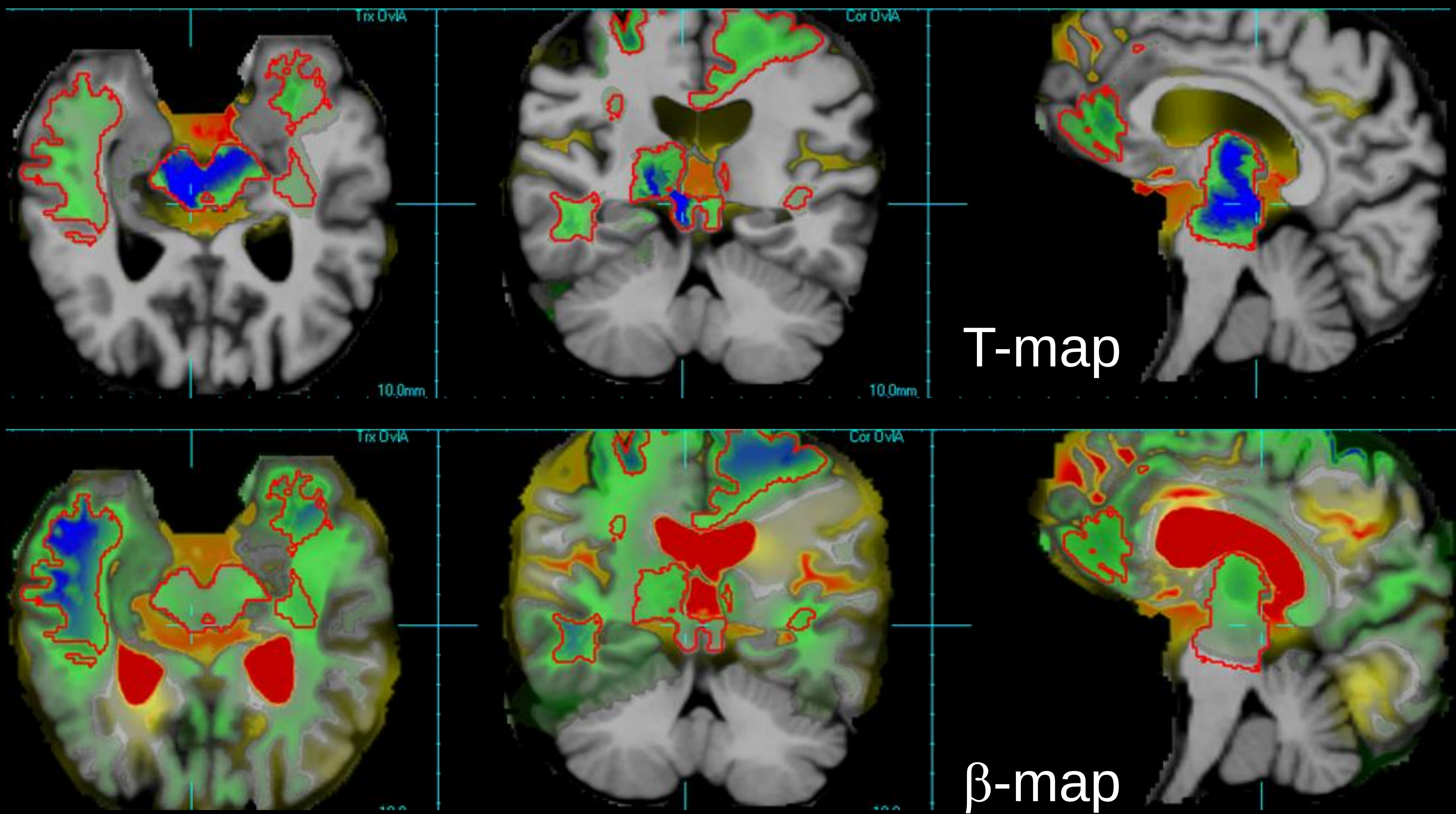
	Age	CDR	MMSE
CN (N=22)	63 7	0	29.3 2.2
FTD (N=22)	63 6	1.12 0.69	23.1 7.0

- Deformation maps created from baseline MRI
- Dependent variables were deformation maps
- Independent variables: group and head size


-UC 0.01
-UC 0.001
-UC 0.0001
-PT 0.05
-PT 0.01
-PT 0.001
BF 0.05
T=2.70
T=6.62

Don’t Forget to Examine the Map of Estimated Effects!

ROI Estimates in Voxel Morphometry



1-50% contraction/expansion

Magnitude of Atrophy

We observed tissue reductions of:

- 34% in the ventromedial frontal region
- 26% in the thalamic region
- 10% in the brainstem region
- 35% in the temporal region (not as significant)
  - Could be poor alignment of structures
  - Inconsistent spatial pattern of atrophy, consistent with considerable variability of clinical features of FTD
- No significant atrophy of parietal or occipital lobes

Validation:
ROI Volumes on 10 FTD vs 10 CN

	CN	FTD	%Reduction	p-value
%Frontal Lobe	34.5 ± 1.0	31.9 ± 2.27	7.5	0.003
%Temporal Lobe	16.3 ± 1.0	16.3 ± 1.0	0	0.85
%Brainstem midsagittal	0.086 ± 7.65E-05	0.076 ± 7.46E-05	11.6	0.006

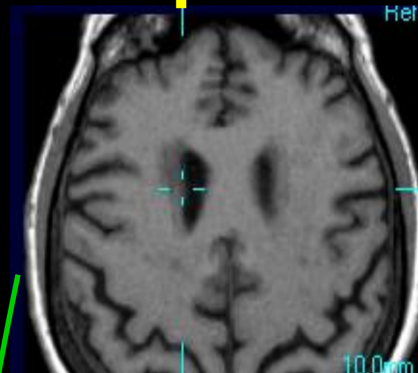
Volumes expressed as % of intracranial volume

Group Differences of Within Subject Changes for Longitudinal Studies

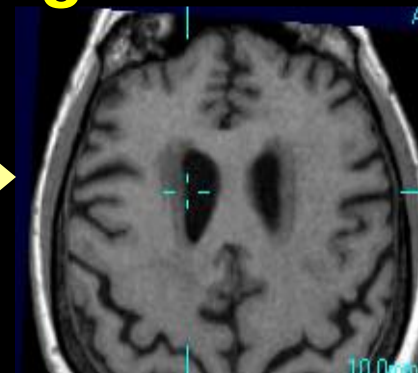
Deformation Morphometry

Creation of Maps of Longitudinal Deformation

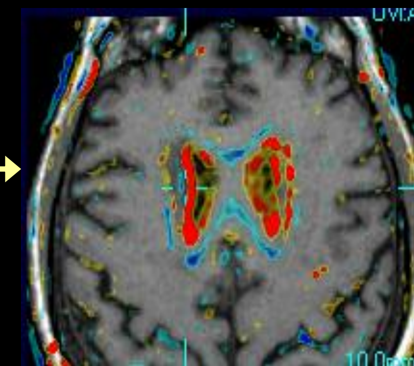
Step 1: Within subject registration between timepoints



timepoint 1

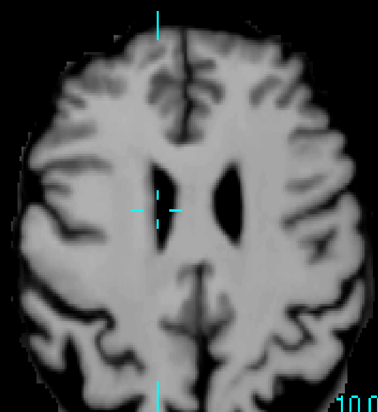


timepoint 2



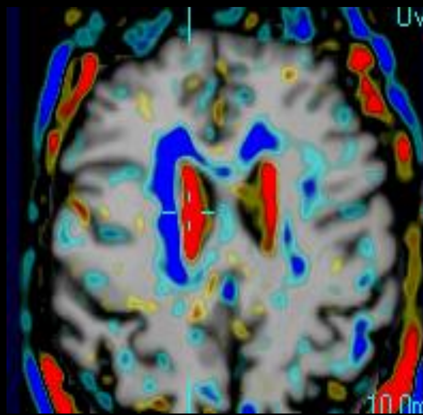
atrophy rate map

Step 2: Subject to atlas registration



atlas

Step 3: Combine registrations

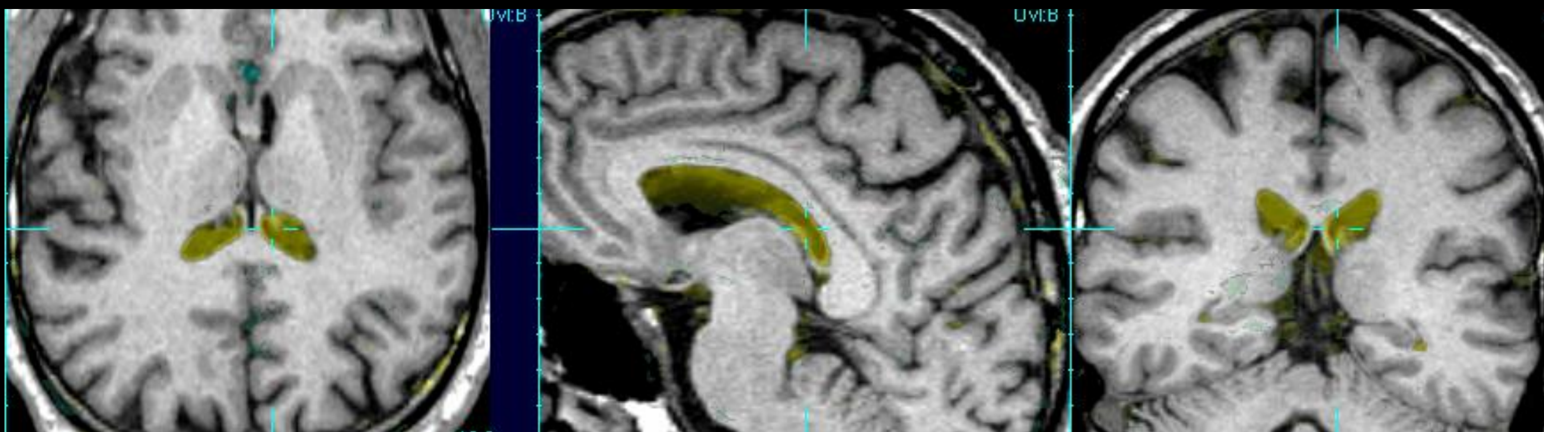


deformation map: atrophy rate in common space

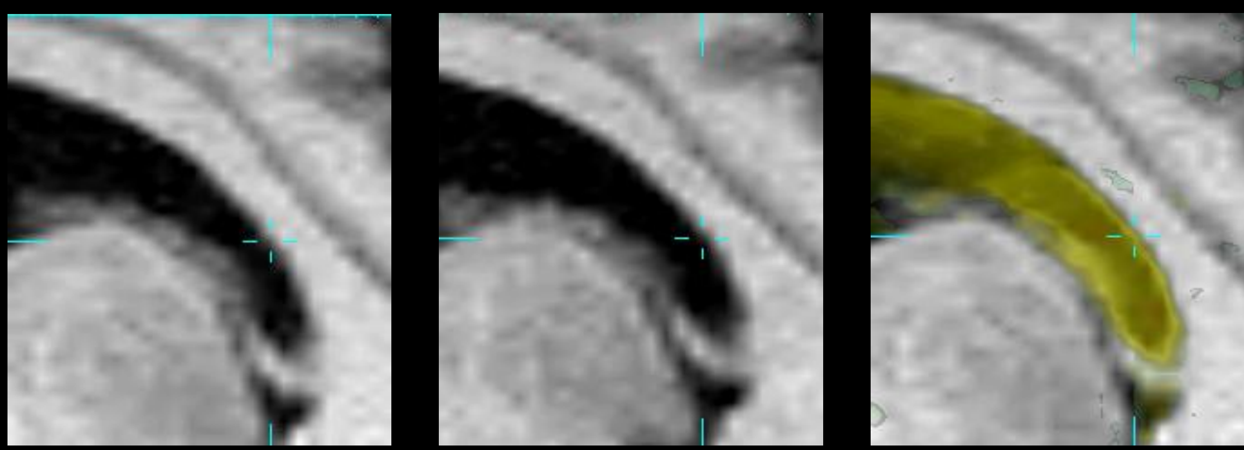
PTSD Question

- Samuelson reported greater cognitive decline in PTSD
  - Delayed facial recognition (WMS-III Faces II)
  - Working memory (Digit Span)
- Is there progressive brain shrinkage with PTSD?
- Longitudinal images and neuropsychological data were analyzed to:
  - Determine the extent to which PTSD accelerates brain atrophy

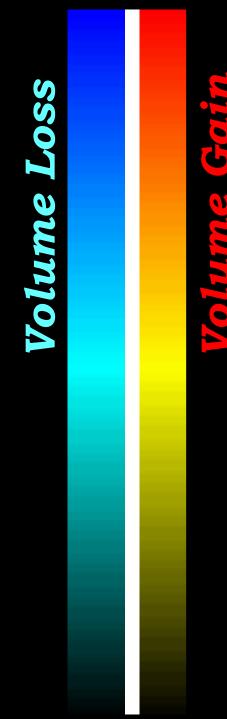
Example PTSD-
Interscan Interval 4.1 yrs



atrophy rate map

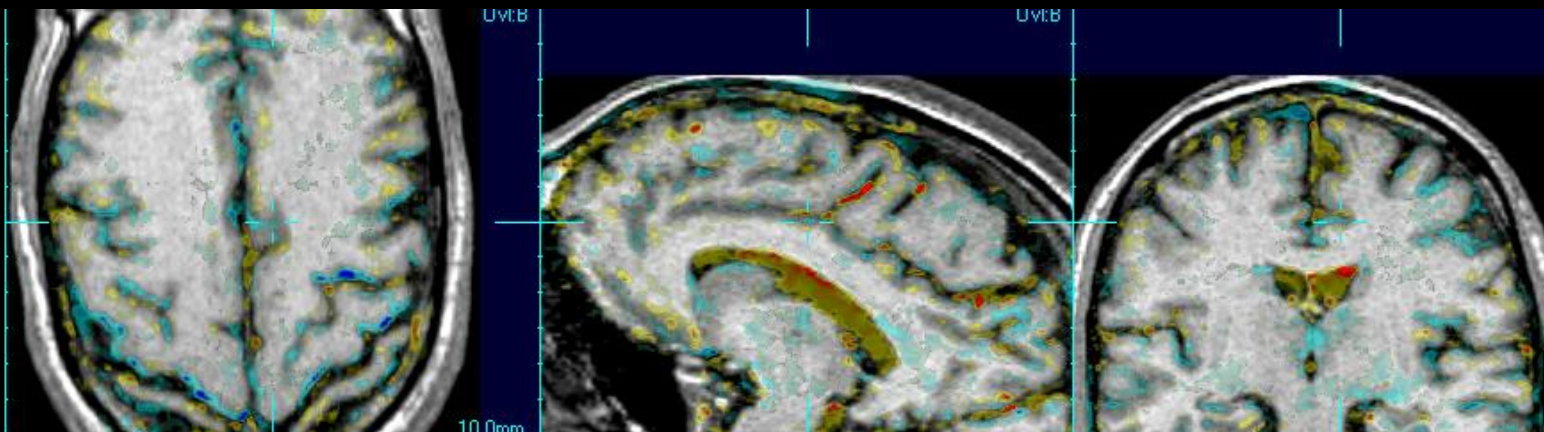


timepoint 1 timepoint 2 atrophy rate map

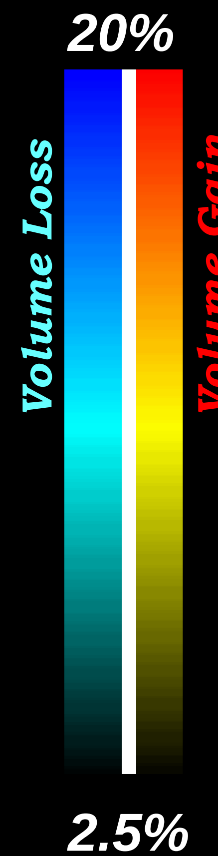


Example PTSD+

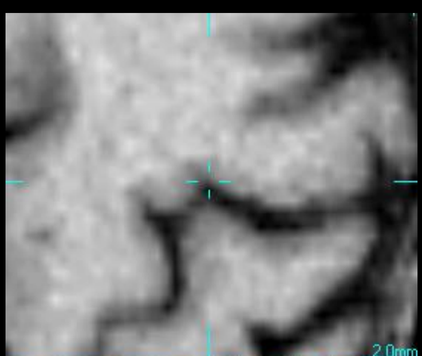
Interscan Interval 3.9 yrs



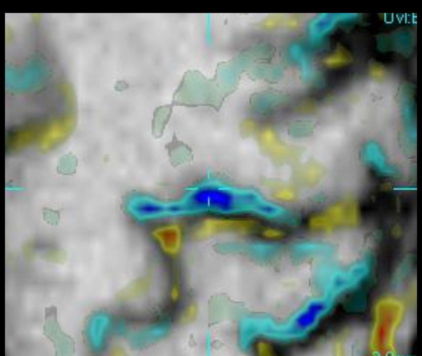
atrophy rate map



timepoint 1

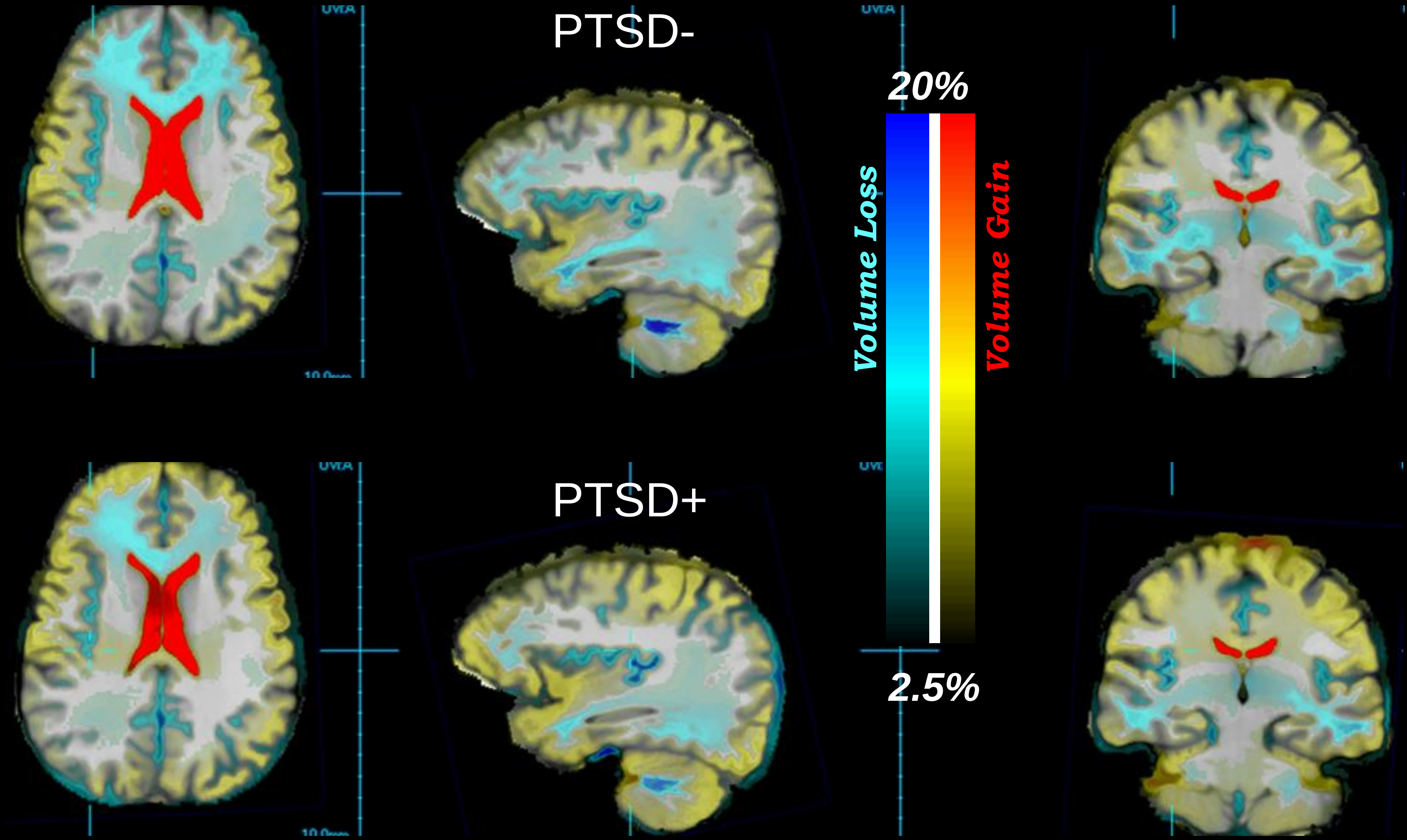


timepoint 2

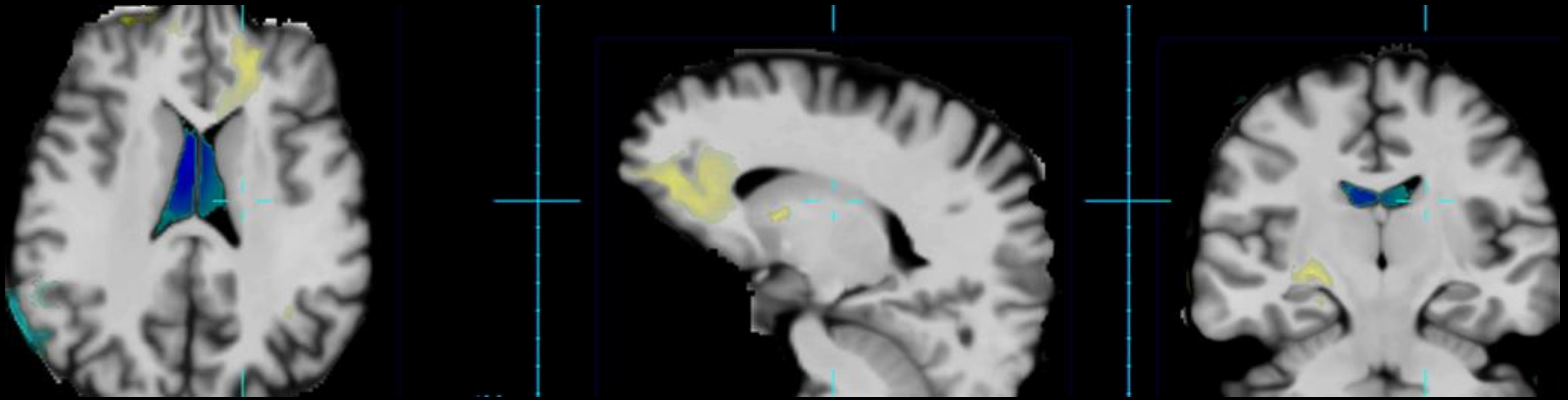


atrophy rate map

Average Rate of Atrophy



PTSD- vs. PTSD+
Map of T-statistics

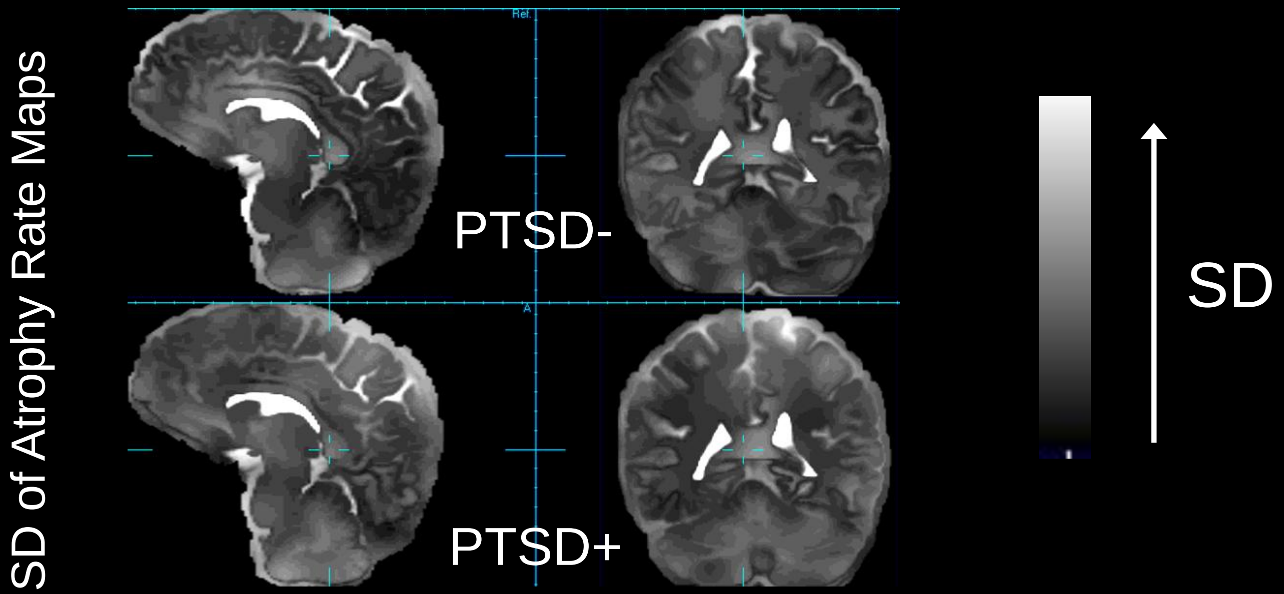


Yellow shows regions of slower brain aging in PTSD+ patients
Blue shows regions of faster brain aging in PTSD+ patients

Small regions of low significance showing opposite effects from expected!

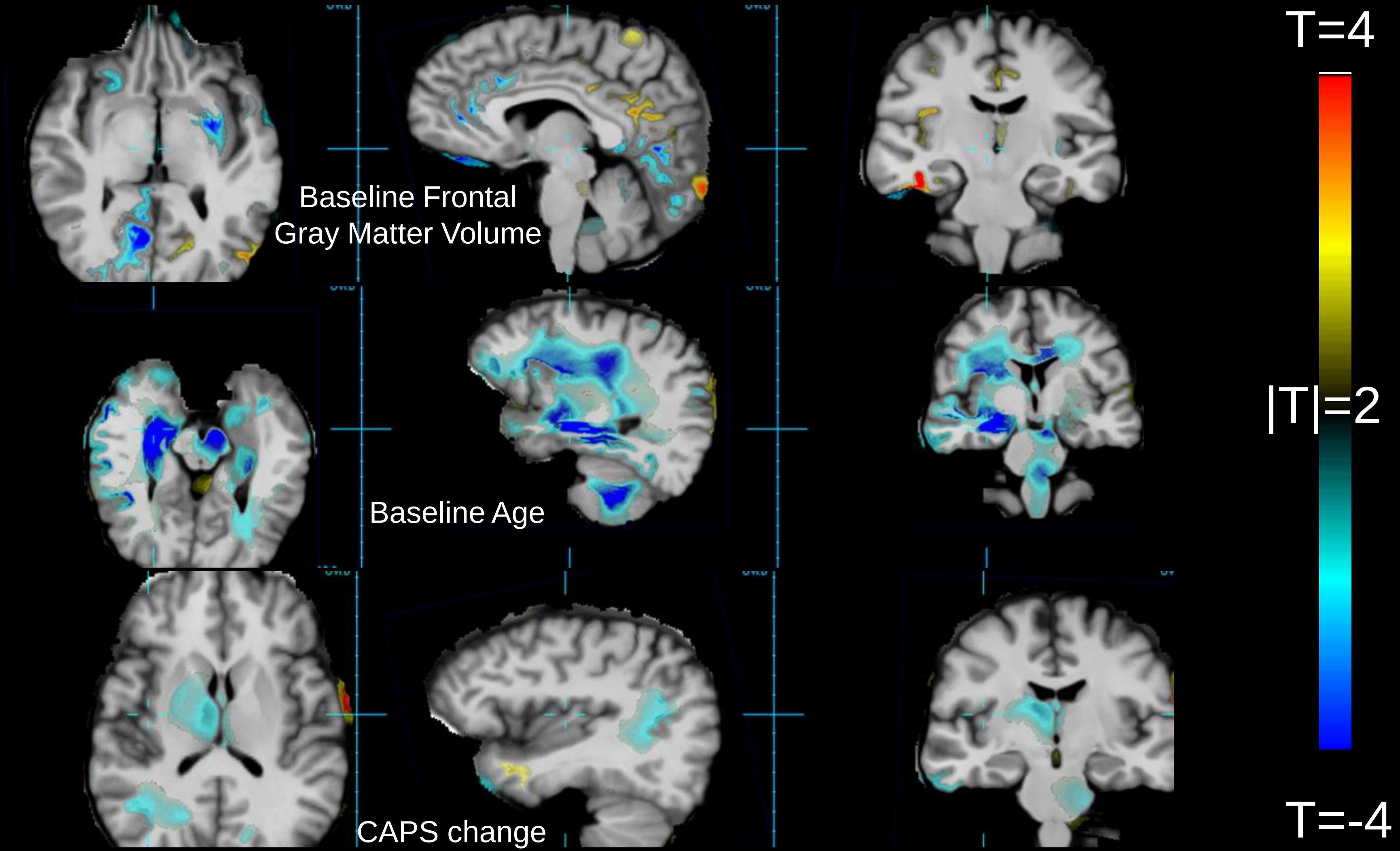
What next?

- Must be greater variability in atrophy rates among PTSD+



- Can we determine measures associated with atrophy rate, account for variability, see PTSD effect?

Atrophy Rate Predictors in PTSD+

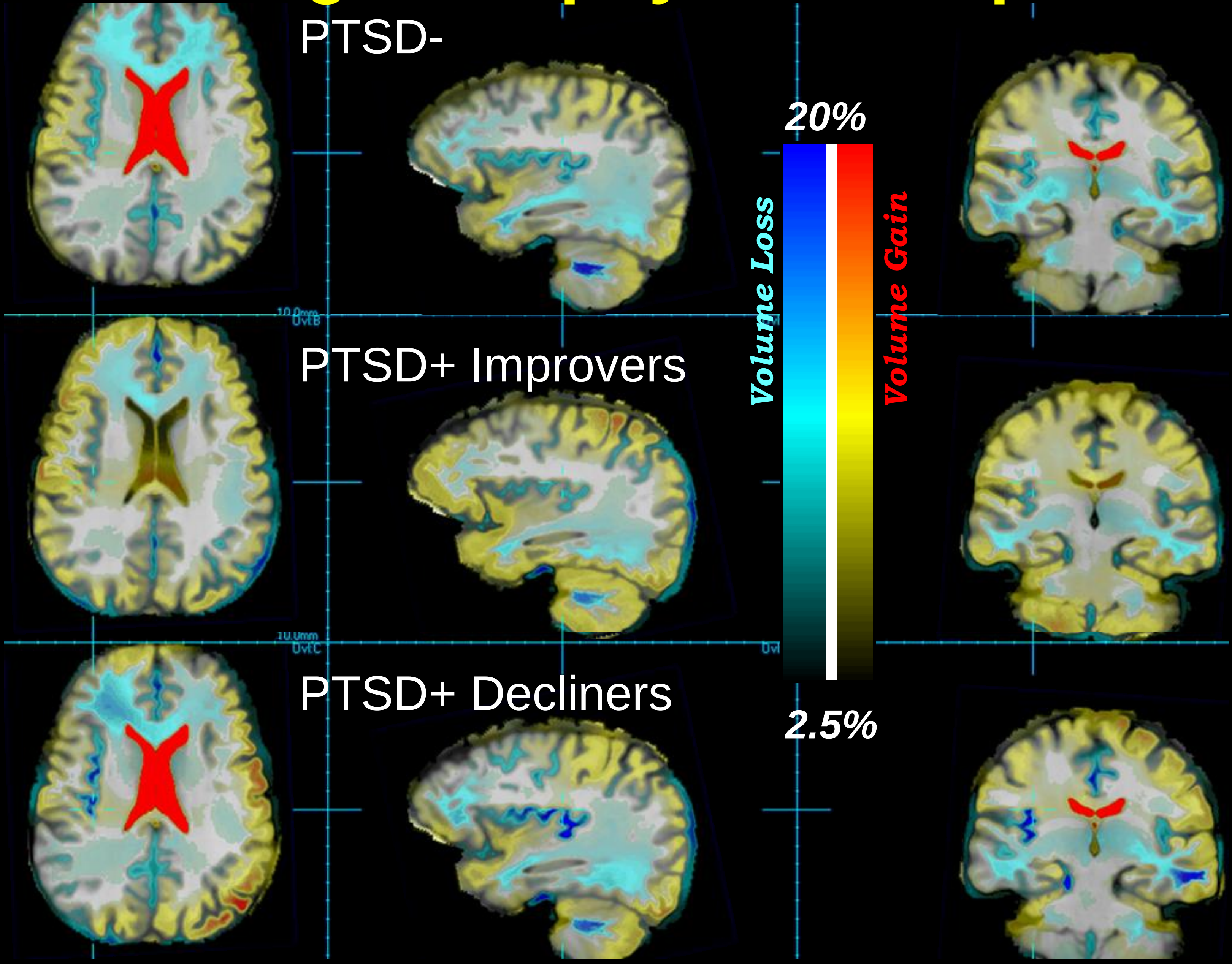


Blue: ↑volumes, ↑age, or ↑ΔCAPS associated with greater atrophy

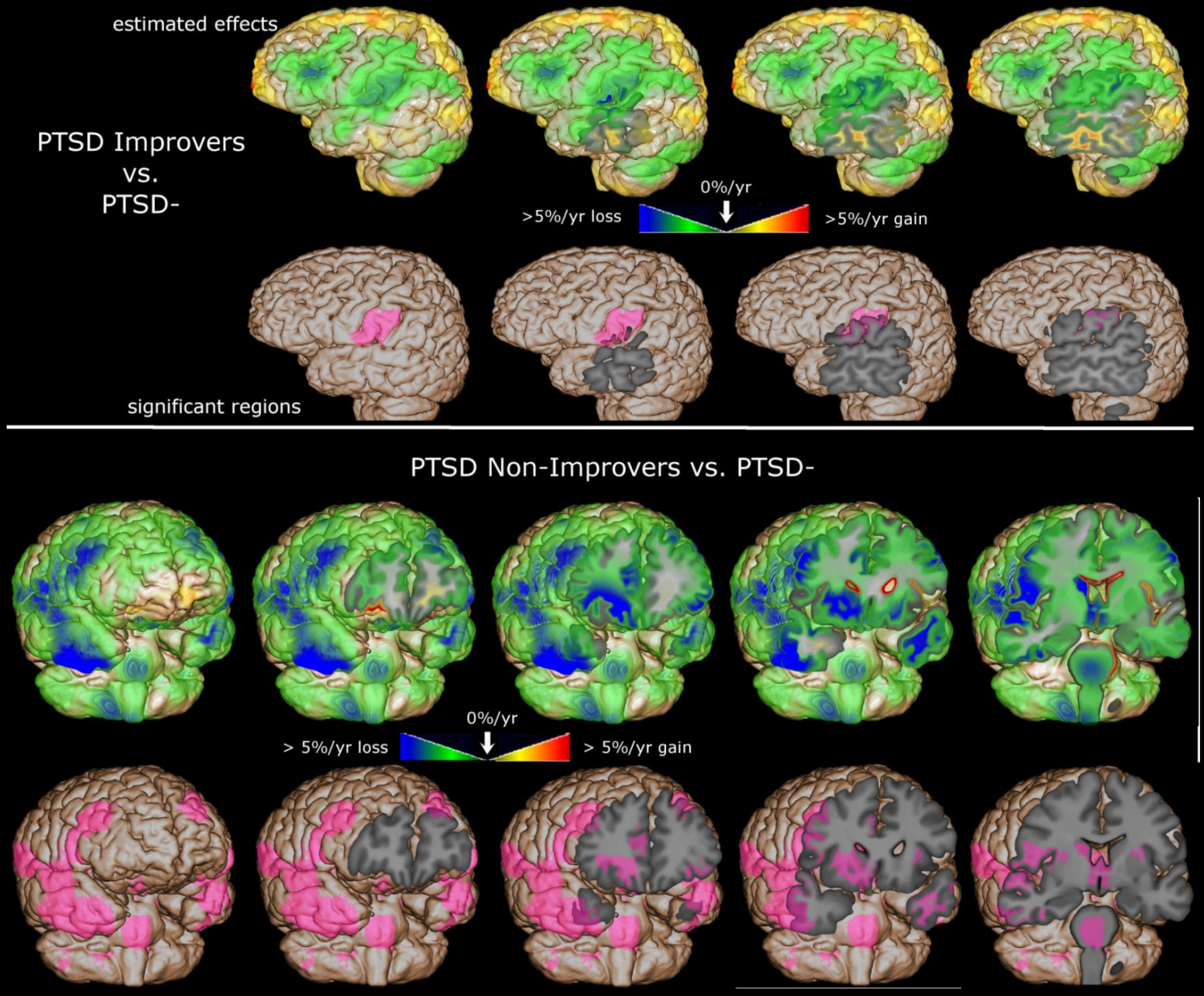
Change in CAPS

- Although all patients still diagnosed as PTSD+ at followup
  - Large variation in course of disease
  - 47 point CAPS increase to 40 point CAPS decrease
  - 6 patients went from full to partial diagnosis
- Subgroup
  - 11 Improvers had 15-40 point CAPS decrease
  - 5 Stable subjects had 6-14 point CAPS decrease
  - 9 Decliners had 2-47 point CAPS increase
- Compare Improvers and Decliners to PTSD- covarying for baseline FGM and age

Average Atrophy Rate Maps



Longitudinal Change in PTSD



Bibliography: deformation morphometry

- Cardenas et al. 2009, J Neurovirol. Jun 4:1-10.
- Pieperhoff et al. 2008, J Neurosci 28(4):828-42.
- Kim et al. 2008, NeuroImage 39(3):1014-1026.
- Cardenas et al., Arch Neurol 64(6):873-877.
- Leow et al. 2009, NeuroImage 45(3):645-655.
- Aljabar et al. 2008, NeuroImage 39(1):348-358.

Structure/Function Relationships

Goals

- Identify patterns of brain atrophy associated with cognitive impairment and future cognitive decline in non-demented elders
- 71 elders studied at baseline and 1 yr
- Examine brain anatomy underlying verbal memory, semantic memory, and executive function

Cognition

- Verbal memory
  - Show list of words
- Semantic memory
  - Object naming
- Executive function
  - Decision making, planning

Cognitive Change

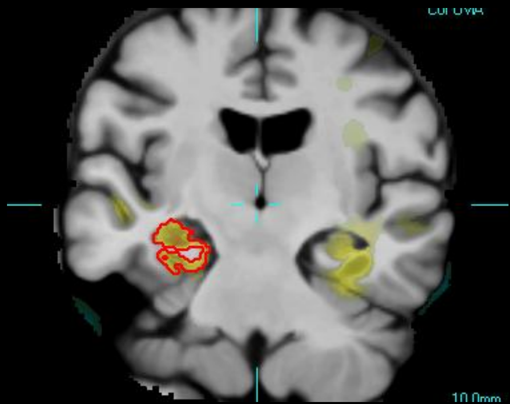
Table 1: Neuropsychological test scores at baseline and 1 year follow-up.

	Delayed Verbal Memory	Semantic Memory	Executive Function
Baseline			
Mean ± SD	99.1 ± 22.0	108.7 ± 13.9	104.3 ± 16.7
(min, max)	(62.1, 139.2)	(72.6, 142.8)	(67.8, 133.3)
1 year follow-up			
Mean ± SD	93.6 ± 20.9*	107.1 ± 13.7	102.7 ± 17.2**
(min, max)	(62.1, 139.2)	(64.8, 135.2)	(61.7, 131.6)

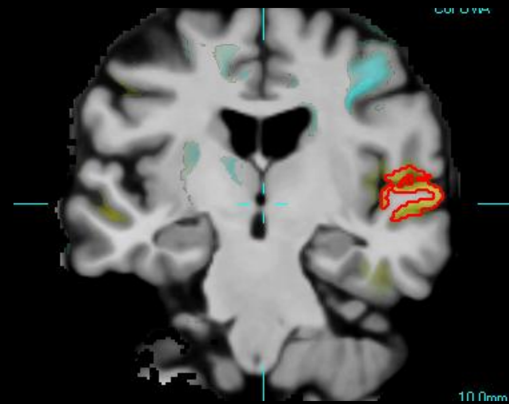
*follow-up < baseline, p=0.0007

****follow-up < baseline, p=0.03**

Anatomy Predicting Cognitive Performance

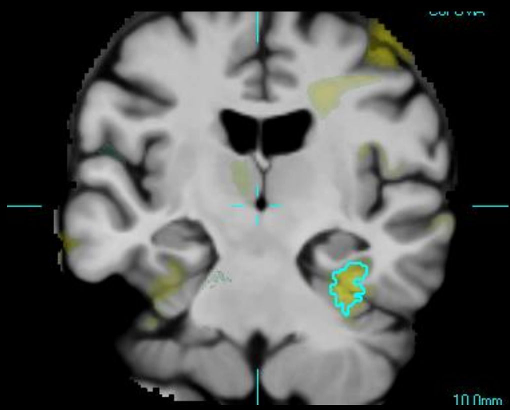


Baseline Memory

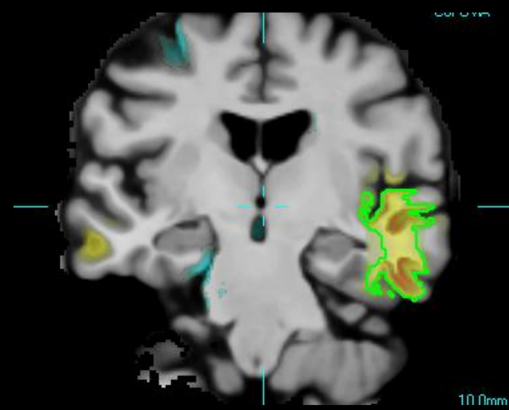


Baseline Object Naming

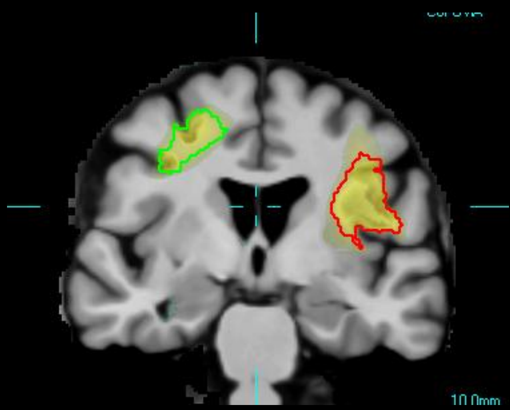
Baseline Executive Function



Memory Decline



Object Naming Decline

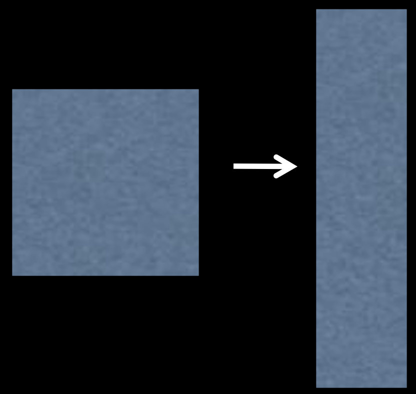


Executive Function Decline

Red/yellow voxels->smaller tissue volume predicts worse cognition or cognitive decline
Blue voxels->greater CSF volume predict worse cognition or cognitive decline

Limitation of Jacobian Determinant

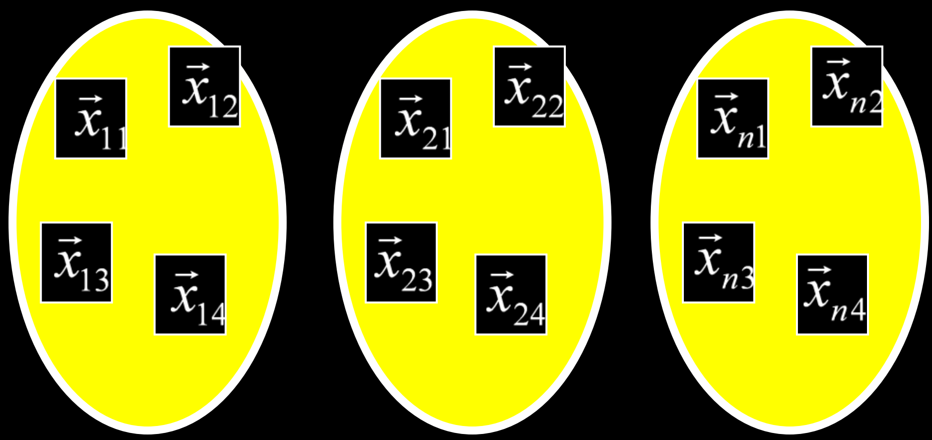
- Information about shape change largely lost
- Orientation specific characteristics lost
- 2D Example:



shape change
no volume change

- Possible solution: examine deformation tensors, full Jacobian matrix, displacement fields

Multivariate voxel-wise



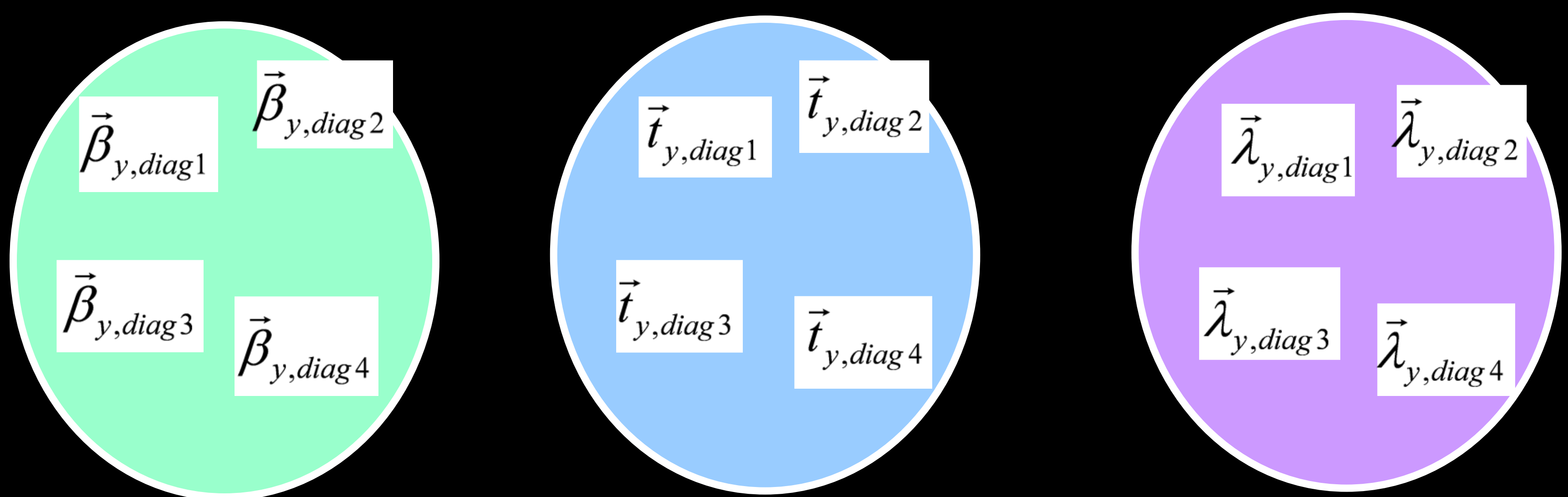
Map 1;
diagnosis 0
age 65
score 16

Map 2;
diagnosis 1
age 68
score 8

Map n;
diagnosis 1
age 73
score 4

$$\begin{bmatrix}\vec{x}_{11}^{\,T}\\ \vec{x}_{21}^{\,T}\\ \vdots\\ \vec{x}_{n1}^{\,T}\end{bmatrix} = \begin{bmatrix}0&65&16&1\\1&68&8&1\\&&\ddots&\\1&73&4&1\end{bmatrix}\begin{bmatrix}\vec{\beta}_{y,diag1}^{\,T}\\ \vec{\beta}_{y,age1}^{\,T}\\ \vec{\beta}_{y,score1}^{\,T}\\ \vec{\beta}_{y,\mathrm{int}1}^{\,T}\end{bmatrix}$$

$$\begin{bmatrix}\vec{x}_{12}^{\,T}\\ \vec{x}_{22}^{\,T}\\ \vdots\\ \vec{x}_{n2}^{\,T}\end{bmatrix} = \begin{bmatrix}0&65&16&1\\1&68&8&1\\&&\ddots&\\1&73&4&1\end{bmatrix}\begin{bmatrix}\vec{\beta}_{y,diag2}^{\,T}\\ \vec{\beta}_{y,age2}^{\,T}\\ \vec{\beta}_{y,score2}^{\,T}\\ \vec{\beta}_{y,\mathrm{int}2}^{\,T}\end{bmatrix}$$



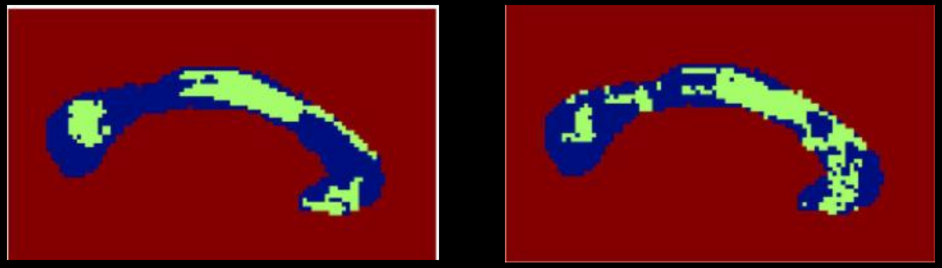
Deformation tensors in HIV

Lepore et al., 2008 IEEE TMI, 27(1):129-141

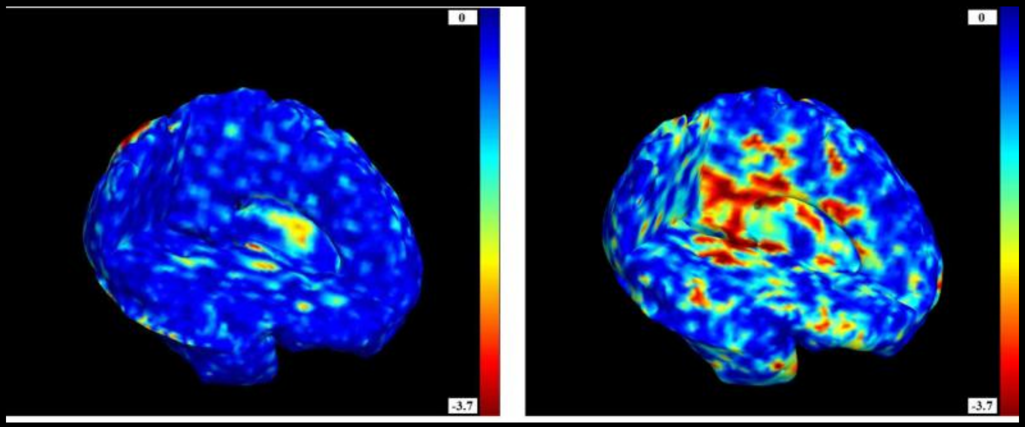
$$\log(S) = \log((J^T J)^{1/2})$$

S is positive definite symmetric; statistics on 6-vector

2D Corpus Callosum Example: green shows $p<0.05$



3D: p-value maps Multivariate shows comparable patterns of atrophy with greater sensitivity



Note there is not complete overlap between methods; univariate and multivariate single modality analyses can be complementary!

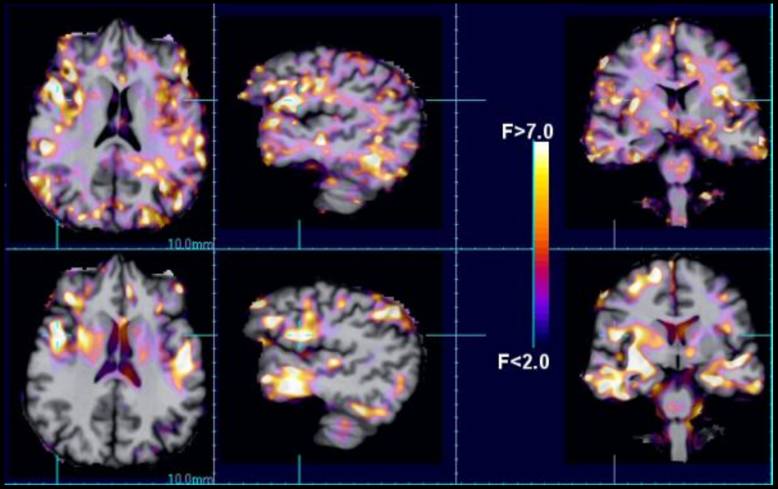
Deformation tensors in alcohol recovery

Studholme and Cardenas., 2007 MICCAI LNCS, 4792:311-318

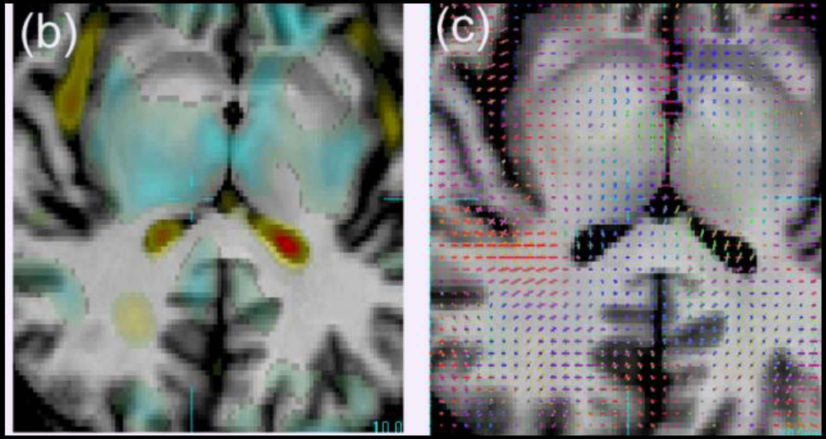
Statistics on 9-vector; all elements from Jacobian matrix encoding longitudinal change in reference coordinates

F-map full Jacobian

F-map |J|



Effect maps: directional patterns of volume change revealed in deep WM and subcortical nuclei



Bibliography: Multivariate Voxel-wise

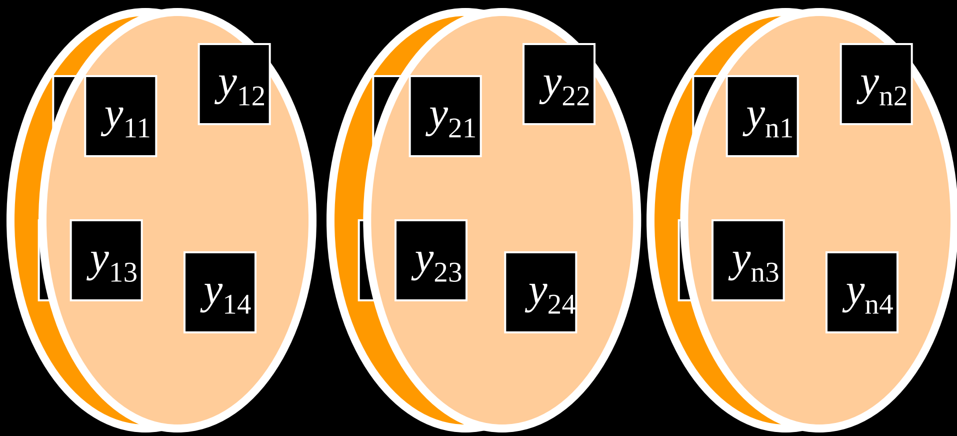
- Gaser et al. 1999, NeuroImage 10:107-113.
- Gaser et al. 2001, NeuroImage 13:1140-1145.
- Thompson and Toga 1997, Medical Image Analysis 1:271-294.
- Worsley et al. 1998, Human Brain Mapping 6:364-367.

Multivariate Multimodality

Multivariate voxel-wise

- Many clinical imaging studies acquire more than one imaging modality
  - T1 structural
  - Spectroscopy
  - Diffusion tensor imaging (DTI)
  - Perfusion imaging
  - fMRI
- Push to integrate all imaging information
- In multivariate voxelwise analyses
  - Dependent variables are deformation maps and other imaging map (e.g., FA)
  - Sensitivity to effects may increase if dependent variables are related (e.g., GM perfusion and GM atrophy)

Multivariate Multimodality



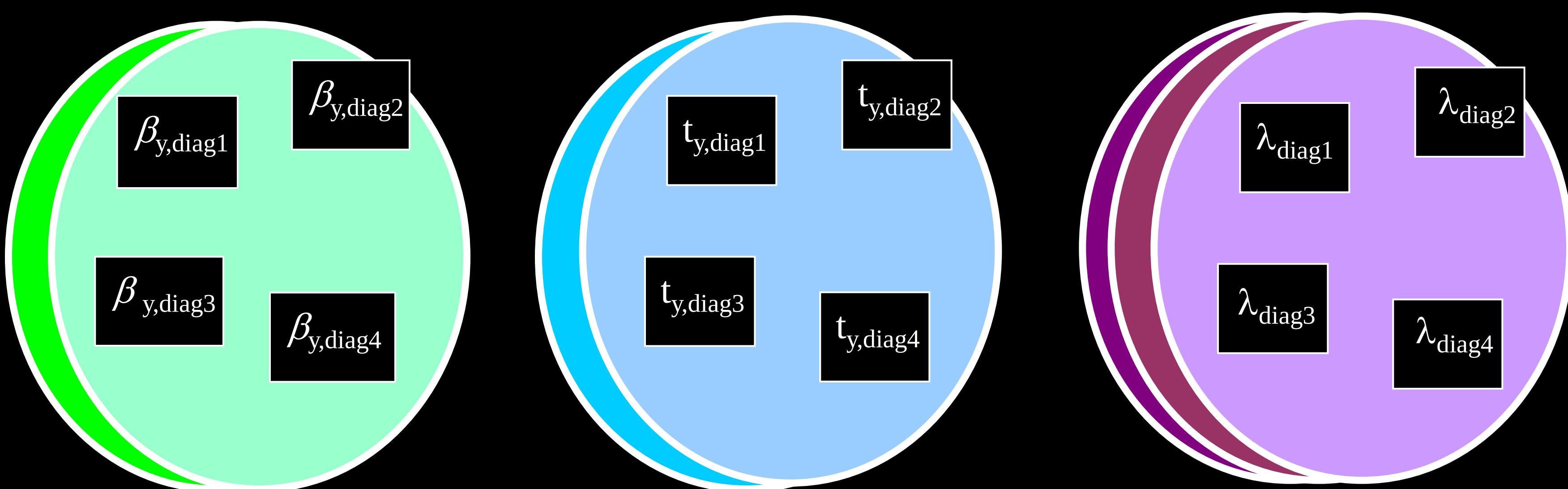
Map 1; diagnosis 0 age 65 score 16

Map 2; diagnosis 1 age 68 score 8

Map n; diagnosis 1 age 73 score 4

$$\begin{bmatrix} y_{11} & z_{11} \\ y_{21} & z_{21} \\ \vdots & \vdots \\ y_{n1} & z_{n1} \end{bmatrix} = \begin{bmatrix} 0 & 65 & 16 & 1 \\ 1 & 68 & 8 & 1 \\ & & \ddots & \\ 1 & 73 & 4 & 1 \end{bmatrix} \begin{bmatrix} \beta_{y,diag1} & \beta_{z,diag1} \\ \beta_{y,age1} & \beta_{z,age1} \\ \beta_{y,score1} & \beta_{z,score1} \\ \beta_{y,\mathrm{int}1} & \beta_{z,\mathrm{int}1} \end{bmatrix}$$

$$\begin{bmatrix} y_{12} & z_{12} \\ y_{22} & z_{22} \\ \vdots & \vdots \\ y_{n2} & z_{n2} \end{bmatrix} = \begin{bmatrix} 0 & 65 & 16 & 1 \\ 1 & 68 & 8 & 1 \\ & & \ddots & \\ 1 & 73 & 4 & 1 \end{bmatrix} \begin{bmatrix} \beta_{y,diag2} & \beta_{z,diag2} \\ \beta_{y,age2} & \beta_{z,age2} \\ \beta_{y,score2} & \beta_{z,score2} \\ \beta_{y,\mathrm{int}2} & \beta_{z,\mathrm{int}2} \end{bmatrix}$$



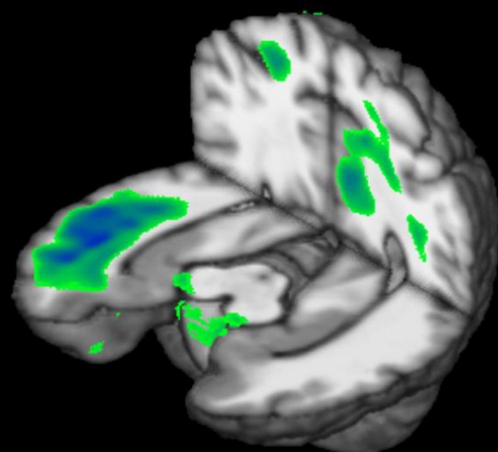
Motivation for Co-Analysis

- Our current implementation of nonlinear registration of structural images uses only T1; no “information” for alignment of within white matter
- DTI provides good imaging of white matter
- Deformation morphometry co-analysis with DTI may reveal more disease-related brain abnormalities than either modality alone
- Is “whole” greater than “sum of parts?”

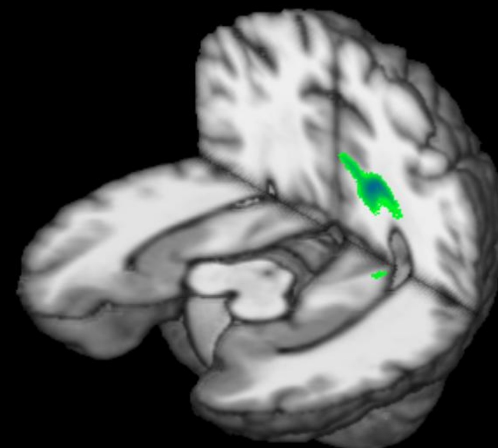
Voxel-wise Statistical Models

- Univariate single modality
  - FA = group + age
  - |J|=group + age
- Univariate multimodality
  - |J| = group + age + FA
- Multivariate multimodality
  - |J| FA = group + age

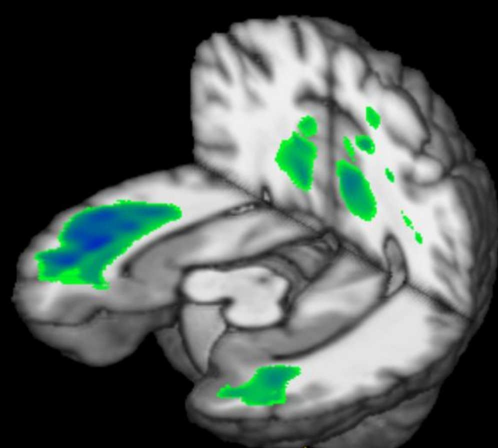
Mild Cognitive Impairment vs. Healthy Elderly



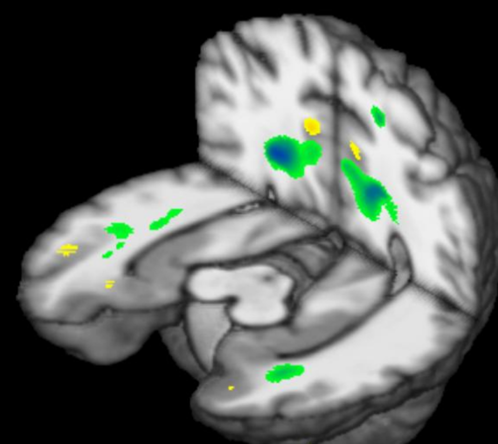
JAC: MCI < CN
univariate cluster $p<0.025$



FA: MCI < CN
univariate cluster $p<0.025$

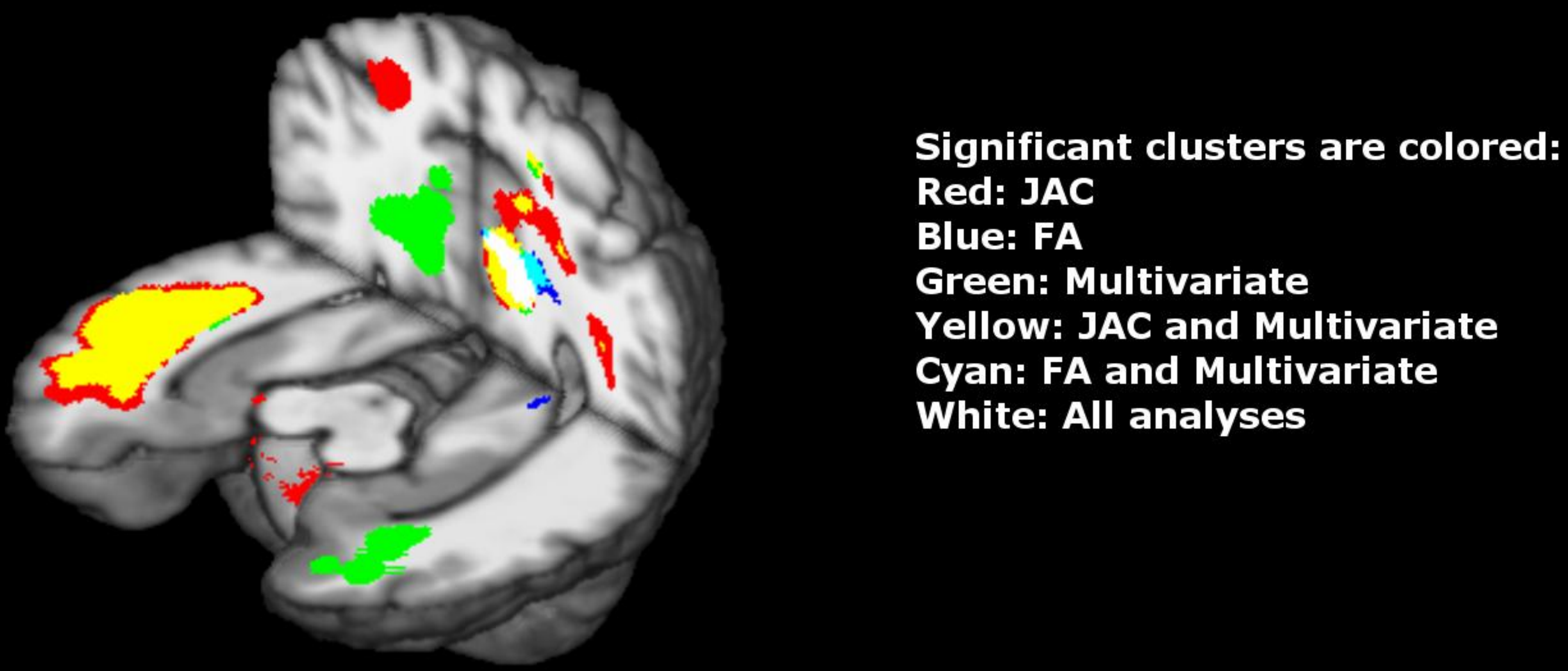


JAC: MCI < CN
multivariate cluster $p<0.05$



FA: MCI < CN
multivariate cluster $p<0.05$

Overlap of Univariate and Multivariate Results



Regions in green highlight better sensitivity of multivariate

Bibliography: Multivariate multimodality

- Friese et al. 2010, J Alzheimers Dis 20(2):477-490.
- Avants et al. 2008, Acad Radiol 15(11): 1360-1375.

Summary

- Computational anatomy is powerful for measuring
  - differences between subjects
  - Group differences in within subject longitudinal change
- Can relate anatomy to clinical and functional variables
- Can facilitate analysis with or in other imaging modalities

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